

Draft Screening Assessment

Phthalate Substance Grouping

**Environment and Climate Change Canada
Health Canada**

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Synopsis

Pursuant to sections 68 and 74 of the *Canadian Environmental Protection Act, 1999* (CEPA), the Minister of the Environment and the Minister of Health have conducted a screening assessment of 14 phthalate esters (phthalates), known collectively as the Phthalate Substance Grouping. Substances in this grouping were identified as priorities for assessment under the Substance Groupings Initiative of the Government of Canada's Chemicals Management Plan (CMP), because they met categorization criteria under section 73 of CEPA or were considered a priority because of human health concerns. This screening assessment follows the August 2015 publication of four state of the science (SOS) reports and an approach document for cumulative risk assessment of phthalates, and it presents information relevant to concluding on the substances in this grouping under section 64 of CEPA.

The Chemical Abstracts Service Registry Numbers (CAS RN¹), Domestic Substances List (DSL) names and acronyms for phthalates in the Phthalate Substance Grouping screening assessment are listed in the table below.

Substances in the Phthalate Substance Grouping

CAS RN	Domestic Substances List name	Acronym	Subgroup
131-11-3	1,2-Benzenedicarboxylic acid, dimethyl ester	DMP	Short-chain
84-69-5	1,2-Benzenedicarboxylic acid, bis(2-methylpropyl) ester	DIBP	Medium-chain
5334-09-8	1,2-Benzenedicarboxylic acid, cyclohexyl 2-methylpropyl ester	CHIBP	Medium-chain
84-64-0	1,2-Benzenedicarboxylic acid, butyl cyclohexyl ester	BCHP	Medium-chain
84-61-7	1,2-Benzenedicarboxylic acid, dicyclohexyl ester	DCHP	Medium-chain
523-31-9	1,2-Benzenedicarboxylic acid, bis(phenylmethyl) ester	DBzP	Medium-chain
68515-40-2	1,2-Benzenedicarboxylic acid, benzyl C7-9-branched and linear alkyl esters	B79P	Medium-chain
27987-25-3	1,2-Benzenedicarboxylic acid, bis(methylcyclohexyl) ester	DMCHP	Medium-chain
71888-89-6	1,2-Benzenedicarboxylic acid, di-C6-8-branched alkyl esters, C7-rich	DIHepP	Medium-chain

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CAS RN	Domestic Substances List name	Acronym	Subgroup
27215-22-1	1,2-Benzenedicarboxylic acid, isooctyl phenylmethyl ester	BIOP	Medium-chain
16883-83-3	1,2-Benzenedicarboxylic acid, 2,2-dimethyl-1-(1-methylethyl)-3-(2-methyl-1-oxopropoxy)propyl phenylmethyl ester	B84P	Medium-chain
68515-48-0 / 28553-12-0	1,2-Benzenedicarboxylic acid, di-C8-10-branched alkyl esters, C9-rich; 1,2-Benzenedicarboxylic acid, diisononyl ester	DINP	See note below ^a
26761-40-0 / 68515-49-1	1,2-Benzenedicarboxylic acid, diisodecyl ester	DIDP	Long-chain
3648-20-2	1,2-Benzenedicarboxylic acid, diundecyl ester	DUP	Long-chain

^a For the purposes of the health review, DINP was included with the medium-chain phthalate esters subgroup, and for the purposes of the ecological review it was included with the long-chain phthalate subgroup (see Environment Canada, Health Canada 2015c for more details).

Phthalates in the Phthalate Substance Grouping assessment were divided into short-chain, medium-chain and long-chain subgroups, depending on the length of the carbon backbone in the ester side-groups. The primary basis for the subgroups from a health hazard perspective was a structure activity relationship (SAR) analysis using studies related to certain events in the mode of action for phthalate-induced androgen insufficiency during male reproductive development in the rat. From an ecological perspective, subgrouping was based primarily on differences in log K_{ow} and water solubility and their resulting effects on bioaccumulation and ecotoxicity. Phthalates within each subgroup are likely to have similar chemical properties, while toxicological properties are largely, but not exclusively, similar. The above table also identifies the subgroup to which each phthalate in the grouping was assigned.

Fourteen additional phthalates on the *Domestic Substances List* were included within the scope of the screening assessment in the context of their potential to contribute to cumulative risk from combined exposure to phthalates. Substance identity information for the additional phthalates considered in this assessment is provided in the table below. Thirteen of the 14 additional phthalates were not assessed individually and therefore no conclusion under section 64 of CEPA is made regarding them. The remaining substance, DEHP, was previously assessed in 1994. However, at that time, there was insufficient information to provide an ecological conclusion. Information has since become available to support a conclusion on its potential to cause harm to the environment.

Additional phthalates considered in the evaluation of cumulative risk

CAS RN	Domestic Substances List name	Acronym	Subgroup
84-66-2	1,2-Benzenedicarboxylic acid, diethyl ester	DEP	Short-chain
131-16-8	1,2-Benzenedicarboxylic acid, dipropyl ester	DPrP	Medium-chain
84-74-2	1,2-Benzenedicarboxylic acid, dibutyl ester	DBP	Medium-chain
85-68-7	1,2-Benzenedicarboxylic acid, butyl phenylmethyl ester	BBP	Medium-chain
84-75-3	1,2-Benzenedicarboxylic acid, dihexyl ester	DnHP	Medium-chain
111381-89-6	1,2-Benzenedicarboxylic acid, heptyl nonyl ester, branched and linear	79P	Medium-chain
27554-26-3	1,2-Benzenedicarboxylic acid, diisooctyl ester	DIOP	Medium-chain
117-81-7	1,2-Benzenedicarboxylic acid, bis(2-ethylhexyl) ester	DEHP	Medium-chain
68648-93-1	1,2-Benzenedicarboxylic acid, mixed decyl and hexyl and octyl diesters	610P	Long-chain
117-84-0	1,2-Benzenedicarboxylic acid, dioctyl ester	DnOP	Long-chain
68515-43-5	1,2-Benzenedicarboxylic acid, di-C9-11-branched and linear alkyl esters	D911P	Long-chain
111381-91-0	1,2-Benzenedicarboxylic acid, nonyl undecyl ester, branched and linear	D911P-2	Long-chain
85507-79-5	1,2-Benzenedicarboxylic acid, diundecyl ester, branched and linear	DIUP	Long-chain
68515-47-9	1,2-Benzenedicarboxylic acid, di-C11-14-branched alkyl esters, C13-rich	DTDP	Long-chain

Results from a CEPA section 71 survey for 2012 determined that 6 of the 28 phthalates being considered in the assessment (DINP, DIDP, DUP, DEHP, D911P and DIUP) were manufactured in and/or imported into Canada in quantities greater than 10 million kg/year, while 7 (BCHP, CHIBP, DBzP, DMCHP, BIOP, DnHP and DPrP) were below the reporting threshold of 100 kg/year. Manufacture and import quantities for the remaining 15 phthalates were in the range of 10 000 to 1 000 000 kg/year. Phthalates are used in a variety of consumer, commercial and industrial products in Canada, including plastics, paints and coatings, adhesives and sealants, automotive parts, electronics, and personal care products.

Water is expected to be the primary receiving medium for phthalates, although some release into air may also occur. When released into the environment, short-chain phthalates are predicted to distribute into water, air and soil, while long-chain phthalates will distribute mainly into soil and sediment with lesser proportions present in the water column. Substances in the medium-chain subgroup exhibit a range of physical-chemical

properties; therefore the predicted distribution among environmental media varies across the substances.

Phthalates biodegrade and are not expected to persist in the environment, although degradation rates vary with phthalate molecular size and physicochemical properties, substrate concentration and environmental conditions. Degradation proceeds more slowly under low oxygen conditions, such as may occur in sediment and soil, potentially increasing exposure times for organisms residing in these media. As well, information on Canadian phthalate use and release patterns suggests that exposure to phthalates in the Canadian environment may be continuous. Because of their rapid biodegradation, exposure to phthalates will be greatest for organisms inhabiting areas close to release sites.

In the environment, phthalates are bioavailable but do not have high bioaccumulation and biomagnification potential given a high rate of biotransformation in biota. Most long-chain phthalates demonstrate low hazard potential in aquatic and terrestrial species, while short- and medium-chain phthalates exhibit moderate to high hazard potential. While narcosis is an important mode of toxic action for phthalates, particularly under short-term exposure, there is strong evidence that some phthalates may also elicit longer-term chronic adverse effects through other, specific modes of action. In particular, some phthalates may have the ability to affect the normal functioning of endocrine systems in organisms. While strong *in vivo* evidence of effects on endocrine systems in aquatic organisms has only been demonstrated for a small number of medium-chain phthalates, evidence suggests that many medium-chain phthalates and some short-chain and long-chain phthalates possess properties that could allow them to adversely influence endocrine activity under some conditions.

Results from an analysis of risk quotients comparing estimated potential exposures for individual phthalates (predicted environmental concentration [PEC]) with their potential for adverse effects (predicted no-effect concentration [PNEC]) determined that 13 phthalates in the Phthalate Substance Grouping present a low risk of causing adverse effects to aquatic species given current exposure levels in the Canadian environment. Two phthalates, B79P and DEHP, have the potential to cause adverse effects in populations of aquatic organisms in Canada at current exposure levels.

In addition, tissue residue analyses were conducted for phthalates having dietary uptake as the primary exposure pathway. The results indicated that maximum tissue concentrations based on solubility limits will be lower than levels associated with adverse acute or chronic lethality effects due to narcosis. A cumulative risk analysis using the Sum of Internal Toxic Units (ITUs) approach determined a total ITU value of 0.2. This value was considered to be conservative as it assumed maximum internal tissue concentrations and highest predicted exposure levels for each of the 28 phthalates examined in the assessment. The results indicate there is no ecological concern due to cumulative effects based on lethality and a narcotic mode of action.

For the general population in Canada, exposure estimates derived from biomonitoring data, when available, were compared to environmental media and food exposure estimates. The principal source of exposure to DMP is expected to be breast milk and food, with indoor air and dust also acting as contributors. Dermal and inhalation (aerosol) exposure to cosmetics and personal care products were also evaluated for adults and infants. Sources of exposure for medium-chain phthalates are indoor air, dust, food and breast milk. Given the information received indicating that a portion of these substances in manufactured items may come in contact with skin, exposure scenarios were identified to characterize dermal exposure for adults and infants. Finally, DIBP and DINP may also be present in children's toys and articles; therefore, oral exposure from mouthing these products was also evaluated. The principal source of exposure to DIDP and DUP for the general population is expected to be house dust (oral ingestion) as well as food and beverages for DIDP (oral ingestion). Exposure scenarios were identified to characterize dermal exposure for adults and children for both long-chain phthalates.

With regard to human health, the health effects data for medium-chain phthalates shows that there is evidence of effects in animal studies that include developmental, reproductive and systemic effects related to the liver and kidneys. Of these, depending on the phthalate in question, the critical effect for risk characterization is developmental effects on males, as the available evidence is strongest for effects on the development of the reproductive system, such as indications of feminization in males, reproductive tract malformations, and effects on fertility related to a relatively well-studied mode of action called the "rat phthalate syndrome" (RPS). This syndrome has been associated with the lowest levels of exposure to this subgroup examined to date in animal studies. The health effects database for short-chain and long-chain phthalate esters shows no evidence of adverse effects on the development of the reproductive system in males. The critical levels selected for risk characterization for DMP were mainly related to mild changes in brain weights after chronic dermal exposure. The health effects database for long-chain phthalates shows that the critical effect for risk characterization is effects on the liver.

Comparisons of estimates of exposure to the 10 medium-chain phthalates in the Phthalate Substance Grouping from various sources, such as environmental media, food, contact with plastic articles (PVC, polyurethane, polyester, etc.), toys and/or personal care products, as well as biomonitoring levels (if available) for all age groups with the appropriate critical effect levels, result in margins of exposures (MOEs) that are considered adequate to address uncertainties in the exposure and health effects databases. Further, these margins are also considered protective of potential reproductive effects not only in males exposed at older life stages but also in females, in addition to effects in other organ systems. Comparisons of estimates of exposure to DMP from environmental media, food, and personal care products, as well as biomonitoring levels for all age groups, with the appropriate critical effect levels, result in MOEs that are considered adequate to address uncertainties in the exposure and health effects databases. Comparisons of estimates for exposure to DIDP and DUP from various sources such as environmental media, food and contact with plastic

articles as well as from biomonitoring levels, as available, with critical effect levels results in margins that are considered adequate to address uncertainties in the exposure and health effects databases. Those margins are also protective of potential limited developmental and reproductive effects of DIDP and DUP toxicity not only in males, but also in females as well as other systemic effects.

Results of the CEPA section 71 industry survey indicate that CHIBP, BHP and BIOP are not currently in use above the reporting threshold of 100 kg, and the likelihood of exposure to the general population in Canada is considered to be low. Hence, the potential risk to human health is considered to be low for these three substances.

On the basis of the information available, there is evidence that phthalates in the medium-chain subgroup have a common mode of action, as they elicit effects on the developing male reproductive system indicative of RPS. Although the MOEs associated with the original 10 medium-chain phthalates included in this assessment are currently considered adequate on an individual substance basis, these MOEs do not address potential risk from concurrent exposure to these and other similar phthalates. As mentioned above, an additional 5 phthalates (BBP, DBP, DEHP, DnHP, and DIOP) were considered in the evaluation of cumulative risk for human health given information indicating that their mode of action is likely to be similar to that of phthalates in the medium-chain subgroup, as well as evidence that they may represent a potential for exposure to the general population of Canada.

A cumulative risk assessment, using a conservative, lower-tiered hazard index (HI) approach has been conducted and indicates no concern for potential cumulative risk of medium-chain phthalates for the general Canadian population, specifically the more sensitive subpopulations (pregnant women/women of childbearing age, infants, and children) at current exposure levels. The HI values for the three subpopulations with the highest estimated exposure levels are all below 1. Hence, further refinement to a higher-tiered assessment is not necessary at this time.

Overall Proposed Conclusion

Considering all available lines of evidence presented in this draft screening assessment, there is low risk of harm to organisms and the broader integrity of the environment from 13 of the phthalates in the Phthalate Substance Grouping (DMP, DIBP, CHIBP, BHP, DHP, DBzP, DMHP, DIHP, BIOP, B84P, DINP, DIDP and DUP); however, there is risk of harm to organisms, but not to the broader integrity of the environment, from 1 phthalate included in the Phthalate Substance Grouping, B79P, and from 1 additional phthalate, DEHP. DEHP was previously assessed by Environment Canada and Health Canada in 1994 under the Priority Substances Assessment Program. The assessment concluded that DEHP is harmful to human health in Canada. However, a conclusion for potential harm to the environment could not be determined at that time because of insufficient information.

It is proposed to conclude that 13 of the 14 substances in the Phthalate Substance Grouping do not meet the criteria under paragraphs 64(a) or (b) of CEPA as they are not entering the environment in a quantity or concentration or under conditions that have or may have an immediate or long-term harmful effect on the environment or its biological diversity or that constitute or may constitute a danger to the environment on which life depends. It is proposed to conclude that the remaining substance in the Phthalate Substance Grouping, B79P, as well as DEHP, meet the criteria under paragraph 64(a) of CEPA as they are entering or may enter the environment in a quantity or concentration or under conditions that have or may have an immediate or long-term harmful effect on the environment or its biological diversity. However, it is proposed to conclude that B79P and DEHP do not meet the criteria under paragraph 64(b) of CEPA as they are not entering the environment in a quantity or concentration or under conditions that constitute or may constitute a danger to the environment on which life depends.

It is proposed to conclude that all 14 phthalates in the Phthalate Substance Grouping do not meet the criteria under paragraph 64(c) of CEPA as they are not entering the environment in a quantity or concentration or under conditions that constitute or may constitute a danger in Canada to human life or health.

Therefore, it is proposed to conclude that B79P and DEHP meet one or more of the criteria set out in section 64 of CEPA. B79P and DEHP have been determined to not meet the persistence and bioaccumulation criteria as set out in the *Persistence and Bioaccumulation Regulations* of CEPA.

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List of abbreviations and acronyms

AF	assessment factor
AFN	Assembly of First Nations
AGD	anogenital distance
AhR	aryl hydrocarbon receptor
AR	androgen receptor
B79P	1,2-benzenedicarboxylic acid, benzyl C7-9-branched and linear alkyl esters - Common name: benzyl octyl phthalate
B84P	1,2-benzenedicarboxylic acid, 2,2-dimethyl-1-(1-methylethyl)-3-(2-methyl-1-oxopropoxy)propyl phenylmethyl ester - Common name: benzyl 3-isobutyryloxy-1-isopropyl-2,2-dimethylpropyl phthalate
BAF	bioaccumulation factor
BBP	1,2-benzenedicarboxylic acid, butyl phenylmethyl ester - Common name: butyl benzyl phthalate
BCF	bioconcentration factor
BCHP	1,2-benzenedicarboxylic acid, butyl cyclohexyl ester - Common name: butyl cyclohexyl phthalate
BIOP	1,2-benzenedicarboxylic acid, isooctyl phenylmethyl ester - Common name: benzyl isooctyl phthalate
BMI	body mass index
CA	concentration addition
CAS RN	Chemical Abstracts Service Registry Number
CBR	critical body residue
CCHS	Canadian Community Health Survey
CEPA	Canadian Environmental Protection Act
CER	creatinine excretion rate
CFIA	Canadian Food Inspection Agency
CHDS	Canadian House Dust Study
CHIBP	1,2-benzenedicarboxylic acid, cyclohexyl 2-methylpropyl ester - Common name: cyclohexyl isobutyl phthalate
CHMS	Canadian Health Measures Survey
CMP	Chemicals Management Plan
CPSD	Consumer Product Safety Directorate, Health Canada
Cr	creatinine
CRA	cumulative risk assessment
CRY	Cryptorchidism
CTV	critical toxicity value
Danish EPA	Danish Environmental Protection Agency
DBP	1,2-benzenedicarboxylic acid, dibutyl ester- Common name: dibutyl phthalate
DBzP	1,2-benzenedicarboxylic acid, bis(phenylmethyl) ester -

	Common name: dibenzyl phthalate
DCHP	1,2-benzenedicarboxylic acid, dicyclohexyl ester - Common name: dicyclohexyl phthalate
DEHP	1,2-benzenedicarboxylic acid, bis(2-ethylhexyl) ester - Common name: diethylhexyl phthalate
DEP	1,2-benzenedicarboxylic acid, diethyl ester - Common name: diethyl phthalate
DI	daily intake
DF	dilution factor
DIBP	1,2-benzenedicarboxylic acid, bis(2-methylpropyl) ester - Common name: diisobutyl phthalate
DIDP	1,2-benzenedicarboxylic acid, diisodecyl ester - Common name: Diisodecyl phthalate
DIHeP	1,2-benzenedicarboxylic acid, di-C6-8-branched alkyl esters, C7-rich- Common name: diisoheptyl phthalate
DINP	1,2-benzenedicarboxylic acid, diisononyl ester or 1,2-benzenedicarboxylic acid, di-C8-10-branched alkyl esters, C9-rich - Common name: Diisononyl phthalate
DIOP	1,2-benzenedicarboxylic acid, diisooctyl ester - Common name: Diisooctyl phthalate
DIY	do-it-yourself
DMCHP	1,2-benzenedicarboxylic acid, bis(methylcyclohexyl) ester - Common name: Bis(methylcyclohexyl) phthalate
DMP	1,2-benzenedicarboxylic acid, dimethyl ester - Common name: Dimethyl phthalate
DnHP	1,2-benzenedicarboxylic acid, dihexyl ester - Common name: dihexyl phthalate
DnOP	1,2-benzenedicarboxylic acid, dioctyl ester - Common name: di-n-octyl phthalate; dioctyl phthalate
DSL	Domestic Substances List
DUP	1,2-benzenedicarboxylic acid, diundecyl ester - Common name: diundecyl phthalate
EC ₅₀	median effective concentration
EHSRD	Environmental Health Science and Radiation Directorate, Health Canada
ER	estrogen receptor
ESRAB	Existing Substances Risk Assessment Bureau, Health Canada
FNBI	First Nations Biomonitoring Initiative
FSAP	Food Safety Action Plan
FUE	fractional urinary excretions
GD	gestion day
HI	hazard index
HQ	hazard quotient
HYP	Hypospadias
IPCS	International Program on Chemical Safety

ITU	internal toxic unit
LC ₅₀	median lethal concentration
LCP	long-chain phthalate esters
LO(A)EL	lowest observed (adverse) effect level
LOD	limit of detection
LOEC	lowest observed effect concentration
MBzP	monobenzylphthalate
MCMHP	mono[2-(carboxymethyl)hexyl]phthalate
MCP	medium-chain phthalate esters
MDL	method detection limit
MECPP	mono(2-ethyl-5-hydroxyhexyl)phthalate
MEHHP	mono(2-ethyl-5hydroxyhexyl)phthalate
MEHP	mono(2-ethyl hexyl)phthalate
MEOHP	mono(2-ethyl-5-oxohexyl)phthalate
MHBP	mono-n-hydroxybutyl phthalate
MIREC	Maternal Infant Research on Environmental Chemicals study
MIREC-CD Plus	Maternal Infant Research on Environmental Chemicals – Child Development Plus study
MnBP	mono-n-butyl phthalate
MNGs	multi-nucleated gonocytes
MoA	mode of action
MOE	margin of exposure
MPE	monoalkyl phthalate ester
MRL	method reporting limit
MW	molecular weight
n	number of samples
ND	not detected
NHANES	National Health and Nutrition Examination Survey
NICNAS	National Industrial Chemicals Notification and Assessment Scheme
NO(A)EL	no observed (adverse) effect level
NOEC	no observed effect concentration
NPRI	National Pollutant Release Inventory
NR	nipple/areolae retention
OECD	Organisation for Economic Co-operation and Development
P4	Plastics and Personal Care Product Use in Pregnancy survey
PEC	predicted environmental concentration
PND	postnatal day
PNEC	predicted no-effect concentration
PPS	preputial separation
PSL1	First Priority Substances List
PSL2	Second Priority Substances List
QSAR	quantitative structure-activity relationship

RAPEX	European Union's Rapid Alert System for Non-Food database
RfV	reference value
ROW	reproductive organ weight
RPS	rat phthalate syndrome
RQ	risk quotient
SAR	structure activity relationship
SCP	short-chain phthalate esters
SOS	state of the science
TP	testicular pathological changes
TR	tissue residue
UER	urinary excretion rate
UF	uncertainty factor
US CHAP	United States Chronic Health Advisory Panel
US CPSC	United States Consumer Product Safety Commission
US EPA	United States Environmental Protection Agency
VTG	Vitellogenin
WHO	World Health Organization
WWTS	wastewater treatment system

1. Introduction

Pursuant to sections 68 and 74 of the *Canadian Environmental Protection Act, 1999* (CEPA) (Canada 1999), the Minister of the Environment and the Minister of Health have conducted a screening assessment of 14 phthalate esters (phthalates), known collectively as the Phthalate Substance Grouping. Substances in this grouping were identified as priorities for assessment under the Substance Groupings Initiative of the Government of Canada's Chemicals Management Plan (CMP) because they met categorization criteria under section 73 of CEPA and/or were considered a priority because of human health concerns (ECCC, HC [modified 2007]).

Certain substances within this grouping have been identified by other jurisdictions as a concern given their potential reproductive and developmental effects in humans. Some phthalates may have common health or ecological effects of concern, so the potential for cumulative risk from combined exposure to these substances was addressed by considering an additional 14 phthalates. The additional 14 phthalates did not meet categorization criteria and were therefore not identified as priorities for assessment. However, they were selected for inclusion in the evaluation of cumulative risk on the basis of information indicating that their mode of action is likely to be similar to that of phthalates in the grouping, as well as evidence that they may represent a potential for exposure to the general population of Canada and to the Canadian environment. Four of the additional phthalates (DBP, BBP, DEHP and DnOP) were previously assessed, on an individual basis, in the First or Second Priority Substances Lists (PSL1 and PSL2) (Environment Canada and Health Canada 1993, 1994a,b, 2000). DBP and BBP were determined to not present a risk to the environment or to human health. DnOP was found to not present a risk to the environment; however, at the time of the assessment, the available information was not sufficient to allow a conclusion in terms of human health. A subsequent report published by Health Canada in 2003 concluded that DnOP did not pose a risk to human health. DEHP was determined to present a risk to human health in Canada; however, there was insufficient information to conclude on the potential for risk to the environment.

Screening assessments focus on information critical to determining whether substances meet the criteria as set out in section 64 of CEPA.² This is done by examining scientific information and incorporating a weight-of-evidence approach and precaution. This draft screening assessment considered information about chemical properties, environmental fate, hazards, uses and exposure, including information submitted by stakeholders.

² A determination of whether one or more of the criteria of section 64 of CEPA are met is based upon an assessment of potential risks to the environment and/or to human health associated with exposures in the general environment. For humans, this includes, but is not limited to, exposures from ambient and indoor air, drinking water, foodstuffs and products used by consumers. A conclusion under CEPA is not relevant to, nor does it preclude, an assessment against the hazard criteria specified in the *Hazardous Products Regulations*, which are part of the regulatory framework for the Workplace Hazardous Materials Information System for products intended for workplace use. Similarly, a conclusion based on the criteria contained in section 64 of CEPA does not preclude actions being undertaken under other sections of CEPA or other Acts.

Relevant data were identified up to April 2016 for the ecological portion and up to July 2016 for the health portion of this draft screening assessment. Empirical data from key studies, as well as some results from models, were used to reach proposed conclusions. When available and relevant, information presented in assessments from other jurisdictions was considered. This draft screening assessment presents the critical information and considerations on which the proposed conclusion is based.

This screening assessment follows the August 2015 publication of four state of the science (SOS) reports (Environment Canada, Health Canada 2015a,b,c,d) for the 14 substances in the Phthalate Substance Grouping, and of a document entitled *Proposed Approach for Cumulative Risk Assessment of Certain Phthalates under the Chemicals Management Plan* (Environment Canada, Health Canada 2015e). These documents were released ahead of the screening assessment in order to allow for the receipt of comments and suggestions from interested parties relating to the proposed cumulative risk assessment approach. Comments received during the 60-day public comment period were taken into consideration during the preparation of this draft screening assessment. The screening assessment summarizes the information presented in the four SOS reports and incorporates relevant new information. As well, the assessment presents risk characterizations for phthalates in the grouping, including analysis of the potential for cumulative risk (ecological risk and risk to human health), and provides proposed conclusions under section 64 of CEPA.

This draft screening assessment was prepared by staff in the Existing Substances Programs at Environment and Climate Change Canada and Health Canada and incorporates input from other programs within these departments. The ecological and human health portions of this draft screening assessment have undergone external written peer review and/or consultation. Comments on the technical portions relevant to the environment were received from Dr. Thomas Backhaus (Faust & Backhaus Environmental Co., Germany), Sonja Bissegger (Royal Military College of Canada), Dr. Valerie Langlois (Royal Military College of Canada), Dr. Lynn McCarty (L.S. McCarty Scientific Research & Consulting, Canada), and Patricia Schmieder (U.S. Environmental Protection Agency). Comments on the technical portions relevant to human health were received from Linda Teuschler (Private consultant – retired from US EPA), Donna Vorhees (The Science Collaborative), Bernard Gadagbui (Toxicology Excellence for Risk Assessment), and Dr. Raymond York (RG York & Associates). While external comments were taken into consideration, the final content and outcome of the screening assessment remain the responsibility of Environment and Climate Change Canada and Health Canada.

The draft screening assessment presents the critical information and considerations on which the proposed conclusions are based. Additional details are provided in the SOS reports and cumulative risk assessment (CRA) document referred to above.

2. Identity of substances

The phthalate esters (phthalates) examined in this draft screening assessment are listed in Table 2-1. Structurally, these phthalates are comprised of a benzene ring with two ester side groups in the *ortho* position.

Substances in the Phthalate Substance Grouping were divided into short-chain, medium-chain and long-chain subgroups, depending on the length of the carbon backbone (i.e., the longest straight chain of carbons) in their ester side-groups. Short-chain phthalates are those with a carbon backbone length of 1 or 2, medium-chain phthalates have a backbone length of 3 to 7 carbons and long-chain phthalates have a backbone length of 8 carbons or greater. The nature of the ester side-groups, which can be linear, branched or cyclic, determines both the identity of the particular phthalate and its physical and toxicological properties.

The primary basis for the subgroups from a health hazard perspective was a structure activity relationship (SAR) analysis using studies related to important events in the mode of action for phthalate-induced androgen insufficiency during male reproductive development in the rat. The effects of phthalate esters for these important events appear to be structure-dependent and highly related to the length and nature of their alkyl chain. From an ecological perspective, subgrouping was based primarily on differences in log K_{ow} and water solubility and their resulting effects on bioaccumulation and ecotoxicity. For the purposes of the health review, DINP was included with the medium-chain phthalates subgroup, while for the purposes of the ecological review, it was considered to align more closely with the long-chain phthalate subgroup.

The chemical structure, molecular weights, water solubilities and octanol-water partition coefficients (log K_{ow}) for phthalates in the Phthalate Substance Grouping are listed in Appendix A. Additional information is provided in Environment Canada, Health Canada (2015a,b,c,d,e), Environment and Climate Change Canada (ECCC 2016) and Health Canada (2016a,b).

In some cases, a read-across approach using data from analogues and the results of quantitative structure-activity relationship (QSAR) models were used to inform the ecological and human health assessments. Model results and descriptions of methods used for analogue selection are provided in Environment Canada, Health Canada (2015a,b,c,d) and Health Canada (2016a,b).

Table 2-1. Substances considered in the Phthalate Substance Grouping screening assessment

Subgroup	Phthalate Substance Grouping Acronym (CAS RN)	Additional phthalates Acronym (CAS RN)
Short-chain	DMP (131-11-3)	DEP (84-66-2)
Medium-chain	DIBP (84-69-5); CHIBP (5334-09-8); BChP (84-64-0); DChP (84-61-7); DBzP (523-31-9); B79P (68515-40-2); DMChP (27987-25-3); DIHepP (71888-89-6); BIOP (27215-22-1); DINP (68515-48-0/28553-12-0) ^a ; B84P (16883-83-3)	DPrP (131-16-8); DBP (84-74-2) ^b ; BBP (85-68-7) ^c ; DnHP (84-75-3); 79P (111381-89-6); DIOP (27554-26-3); DEHP (117-81-7) ^b
Long-chain	DIDP (26761-40-0/68515-49-1); DUP (3648-20-2)	610P (68648-93-1); DnOP (117-84-0) ^b ; D911P (68515-43-5); D911P-2 (111381-91-0); DIUP (85507-79-5); DTDP (68515-47-9)

Abbreviation: CAS RN, Chemical Abstracts Service Registry Number

^a DINP was considered as a medium-chain phthalate for the purposes of the health assessment, and as a long-chain phthalate for the purposes of the ecological assessment.

^b Included in the PSL1

^c Included in the PSL2

3. Physical and chemical properties

The chemical properties of substances in the Phthalate Substance Grouping are primarily determined by the molar volume of the substance and the length of the alkyl side-chains substituted on the diester groups (Cousins et al. 2003). Substances in the grouping are oily liquids at typical ambient temperatures. Melting points for substances in the grouping vary between -64°C and 66°C, and boiling points are between 205°C and 463°C. Therefore, some phthalates in the grouping have the potential to be present in the solid state at low temperatures in the environment. In general, water solubility and vapour pressure decrease with increasing molar volume and alkyl side-chain length, while the tendency to adsorb to organic materials and particulates increases. For example, the short-chain phthalate DMP has very high water solubility (4000 mg/L), moderate vapour pressure (0.4 Pa) and low partition coefficients ($\log K_{ow}$ 1.6, $\log K_{oc}$ between 1.9 and 2.5), while the long-chain phthalate DIDP has very low water solubility and vapour pressure (1.7×10^{-4} mg/L, 6.7×10^{-5} Pa) and high to very high partition coefficients ($\log K_{ow} > 8$, $\log K_{oc}$ 5.5). Medium-chain phthalates display a range of chemical property values intermediate between those of short- and long-chain phthalates. Detailed information about chemical property values for substances in the Phthalate Substance Grouping is provided in the SOS reports (Environment Canada, Health Canada 2015a,b,c,d).

4. Sources

Anthropogenic activities are the major source of phthalates in the environment. An industry survey issued pursuant to section 71 of CEPA was conducted in 2013 to obtain information on quantities in commerce in 2012 for substances in the Phthalate Substance Grouping and for the additional phthalates in Canada (Canada 2013). Results are presented in Tables 4-1 and 4-2 (Environment Canada 2014). Because of the targeted nature of the survey, reported use quantities may not fully reflect all uses in Canada.

Table 4-1. Information on Canadian quantities (for the year 2012) for phthalates in the Phthalate Substance Grouping submitted pursuant to a CEPA section 71 survey

Phthalate Acronym	Total manufacture (kg) ^a	Total import (kg) ^a	Total export (kg) ^a
DMP	< reporting threshold ^b	10 000–100 000	< reporting threshold
DIBP	< reporting threshold	10 000–100 000	< reporting threshold
DCHP	< reporting threshold	< 10 000	< reporting threshold
DIHepP	< reporting threshold	< 10 000	< reporting threshold
B79P	< reporting threshold	100 000–1 000 000	100 000–1 000 000
B84P	< reporting threshold	100 000–1 000 000	100 000–1 000 000
DINP	1 000 000–10 000 000	> 10 000 000	1 000 000–10 000 000
DIDP	10 000–100 000	1 000 000–10 000 000	100 000–1 000 000
DUP	> 10 000 000	100 000–1 000 000	1 000 000–10 000 000
BCHP	< reporting threshold	< reporting threshold	< reporting threshold
CHIBP	< reporting threshold	< reporting threshold	< reporting threshold
DBzP	< reporting threshold	< reporting threshold	< reporting threshold
DMCHP	< reporting threshold	< reporting threshold	< reporting threshold
BIOP	< reporting threshold	< reporting threshold	< reporting threshold

^a Values reflect quantities reported in response to the survey conducted under section 71 of CEPA (Environment Canada 2014). See survey for specific inclusions and exclusions (schedules 2 and 3).

^b Reporting threshold: a total quantity greater than 100 kg of a substance, at a concentration equal to or above 0.001% by weight (w/w%) (Canada 2013).

Table 4-2. Information on Canadian quantities (for the year 2012) for additional phthalates submitted pursuant to a CEPA section 71 survey

Phthalate Acronym	Total manufacture (kg) ^a	Total import (kg) ^a	Total export (kg) ^a
BBP	< reporting threshold ^b	100 000–1 000 000	100 000–1 000 000
DBP	< reporting threshold	100 000–1 000 000	10 000–100 000
DEHP	1 000 000–10 000 000	100 000–1 000 000	10 000–100 000
DIOP	< reporting threshold	< 10 000	0
DEP	< reporting threshold	< 10 000	< 10 000
79P	< reporting threshold	10 000–100 000	< reporting threshold
610P	100 000–1 000 000	100 000–1 000 000	100 000–1 000 000

Phthalate Acronym	Total manufacture (kg)^a	Total import (kg)^a	Total export (kg)^a
DnOP	< reporting threshold	100 000–1 000 000	< reporting threshold
D911P-2	< reporting threshold	10 000–100 000	< reporting threshold
D911P	> 10 000 000	100 000–1 000 000	1 000 000–10 000 000
DTDP	< reporting threshold	100 000–1 000 000	< reporting threshold
DIUP	1 000 000–10 000 000	100 000–1 000 000	100 000–1 000 000
DnHP	< reporting threshold	< reporting threshold	< reporting threshold
DPrP	< reporting threshold	< reporting threshold	< reporting threshold

^a Values reflect quantities reported in response to the survey conducted under section 71 of CEPA (Environment Canada 2014). See survey for specific inclusions and exclusions (schedules 2 and 3).

^b Reporting threshold: a total quantity greater than 100 kg of a substance, at a concentration equal to or above 0.001% by weight (w/w%) (Canada 2013).

5. Uses

The results of a CEPA section 71 industry survey for 2012 included information on uses for 21 phthalates (Environment Canada 2014). No information was available for the other 7 substances.

Canadian uses identified for phthalate substances included in the Phthalate Substance Grouping are summarized in the SOS reports (Environment Canada, Health Canada 2015a,b,c,d). For the additional phthalates, Canadian uses are identified in Tables 5-1, 5-2 and 5-3. Additionally, international uses of phthalates can also be found in the SOS documents (Environment Canada, Health Canada 2015a,b,c,d).

Table 5-1. Summary of Canadian uses for selected additional phthalates, as reported pursuant to a CEPA section 71 survey^a

Major uses ^b	DBP	BBP	DEHP	DIOP	DEP	79P
Adhesives and sealants	✓	✓	–	✓	–	✓
Paints and coatings	✓	✓	✓	–	–	–
Electrical/electronics	✓	✓	–	–	–	–
Building materials	✓	✓	✓	–	–	–
Automotive and transportation products	–	✓	✓	–	–	✓
Lubricants and greases	–	–	✓	–	–	–
Printing inks	✓	✓	–	–	–	–
Fabric and textiles	✓	✓	✓	–	–	–
Personal care products	–	–	–	–	✓	–
Children's toys and childcare articles ^c	✓	✓	✓	–	–	–
Plastic and rubber materials	✓	✓	✓	–	✓	–

- This use was not identified for this substance.

^a Use information for phthalate substances reported to be in commerce in Canada (Environment Canada 2014)

^b All information obtained from section 71 industry survey conducted under CEPA (Environment Canada 2014).

^c Presence of DBP, BBP, and DEHP in these types of products is currently restricted to ≤1,000 mg/kg (*Phthalates Regulations* under the *Canada Consumer Product Safety Act* [Canada 2016]).

Table 5-2. Summary of Canadian uses for selected additional phthalates, as reported pursuant to a CEPA section 71 survey^a (continued)

Major uses ^b	610P	DnOP	D911P-2	D911P	DTDP	DIUP
Adhesives and sealants	–	–	✓	–	–	✓
Paints and coatings	–	–	–	–	–	–

Major uses ^b	610P	DnOP	D911P-2	D911P	DTDP	DIUP
Electrical/electronics	–	✓	✓	✓	✓	✓
Building materials	–	–	–	–	–	–
Automotive and transportation products	✓	–	✓	✓	–	✓
Lubricants and greases	–	–	–	–	✓	–
Printing inks	–	–	–	–	–	–
Fabric and textiles	–	–	–	–	–	–
Personal care products	–	–	–	–	–	–
Children's toys and childcare articles	–	–	–	–	–	–
Plastic and rubber materials	✓	✓	–	✓	–	✓

- This use was not identified for this substance.

^a Use information for phthalate substances reported to be in commerce in Canada (Environment Canada 2014).

^b All information obtained from section 71 industry survey conducted under CEPA (Environment Canada 2014).

Table 5-3. Notifications in Canada for selected additional phthalates^a

	BBP	DBP	DEHP ^h	DnHP	DIOP
Food packaging materials ^b	✓	✓	✓	–	✓
Drug Product Database ^c	–	✓	–	–	–
Natural Health Products Ingredients Database ^d	–	✓	–	–	–
Licensed Natural Health Products Database being present as a non-medicinal ingredient in natural health products in Canada ^e	–	✓	–	–	–
Notified to be present in cosmetics, based on notifications submitted under the <i>Cosmetic Regulations</i> , Canada ^f	–	✓	–	–	–
Formulant in pest control products registered in Canada ^g	✓	–	–	–	–

- Notifications for this use have not been received for this substance.

^a Select additional phthalates are those phthalate substances included in the CRA for human health only.

^b September 2014 emails from the Food Directorate, Health Canada to the Risk Management Bureau, Health Canada; unreferenced.

^c DPD [modified 2014].

^d NHPID [modified 2014].

^e LNHPD modified 2014, September 2014 email from the NNHPD, Health Canada, to the Risk Management Bureau, Health Canada; unreferenced.

^f July 2015 email from the Consumer Product Safety Directorate (CPSD), Health Canada, to Existing Substances Risk Assessment Bureau (ESRAB), Health Canada; unreferenced.

^g April 2012 email from the Pest Management Regulatory Agency, Health Canada, to the Risk Management Bureau, Health Canada; unreferenced.

dSAR – Phthalate Substance Grouping

^h DEHP is on the List of Prohibited and Restricted Cosmetic Ingredients in Canada (Health Canada [modified 2011a]) and was not reported as used in Canada (July 2015 email from the CPSD, Health Canada to ESRAB, Health Canada; unreferenced).

6. Releases to the environment

There are no known major natural sources of phthalates, and releases to the environment are associated with anthropogenic activities. Releases may occur during the manufacture and processing of phthalates, including transportation and storage, as well as during production, use and disposal of products that contain phthalates (e.g., release of phthalates into wastewater systems from use of cosmetics). Phthalates are not chemically bound to polymer matrices during processing activities and can migrate to the surface of polymer products over time. The rate of this migration is expected to be slow and will be counteracted by chemical and physical attractive forces that work to hold the phthalates within polymers. Given their consumer and industrial applications, releases of phthalates to the environment are expected to occur primarily to air and to water.

Information on releases of phthalates in Canada is limited. Six phthalates (DMP and five of the additional phthalates, i.e., DEP, DBP, BBP, DEHP and DnOP) are reportable to the National Pollutant Release Inventory (NPRI), where all reported releases were to air (NPRI 2010-2014). For the section 71 survey, many submissions indicated no or unknown releases (Environment Canada 2014).

Further discussion on the potential for environmental release is provided in Environment Canada, Health Canada (2015a,b,c,d).

7. Environmental fate and behaviour

7.1 Environmental distribution

The EQC Level III fugacity model (New EQC 2011) was used to predict the environmental mass-fraction distributions of the short-, medium-, and long-chain phthalates. Environmental distribution trends were largely driven by the phthalates' capacity to solubilize in water, volatilize or adsorb to particles, where smaller more soluble substances tended to be associated with the air and aquatic media, and larger substances with limited water solubility tended to adsorb to sediment or remain in soil. The EQC model results show that the short-chain phthalates distribute into water, soil and air, but not into sediment, the medium-chain phthalates distribute more evenly between water and sediment, and the long-chain phthalates distribute mainly into sediment, with a lesser proportion remaining in water. Soil was predicted to be an important receiving compartment for the medium- and long-chain phthalates (that is, if released to air or soil, the medium- and long-chain phthalates primarily remain in soil). The results from the Level III fugacity modelling showing percent distribution into water, soil and sediment based on simulated release into each compartment are summarized in ECCC (2016).

On the basis of the known uses and releases of phthalates (see Sections 5 and 6), water is considered to be the key receiving environmental compartment of phthalates.

7.2 Environmental persistence

The degradation of phthalates is well-characterized, and phthalates are known to be degraded by abiotic and biotic processes. Numerous studies have been conducted for the short-chain phthalates DMP and DEP, the medium-chain phthalates DIBP, DCHP, B79P, BBP, DBP and DEHP, and the long-chain phthalates DIDP, DUP and DINP. Many of these studies have been used to characterize the less-studied phthalates, including the medium-chain phthalates BChP, CHIBP, DBzP, DMChP, BIOP, B84P, 79P, DIOP, DnHP, DPrP and DIHepP, and the long-chain phthalates 610P, D911P, D911P-2, DTDP, DIUP and DnOP. Summaries of degradation studies and QSAR modelling are available in the SOS reports (Environment Canada, Health Canada 2015a,b,c,d) and in ECCC (2016).

Abiotically, phthalates undergo hydrolysis, which tends to be slow, and relatively fast photolysis (Peterson and Staples 2003). It is biodegradation—particularly in aerobic conditions, by micro-organisms, including the green microalgae species (Chang et al. 2005; Yan and Pan 2004; Yan et al. 2002), phytoplankton (Li et al. 2007) and fungi (Ganji et al. 1995; Sivamurthy et al. 1991; Engelhardt et al. 1977; Kim and Lee 2005; Lee et al. 2007; Kim et al. 2002a, 2003, 2007)—that contributes most to the breakdown of these substances in the environment. The observed biodegradation rates vary and are influenced by the molecular size and physicochemical properties of phthalates, substrate concentration and environmental conditions. The (Q)SAR model-generated data are in agreement with the experimental data. The biodegradation of phthalate

esters releases monoalkyl phthalate esters (MPEs) into the environment (McConnell 2007). Most studies suggest that biodegradation rates of MPEs proceed faster than those of phthalate esters (Peterson and Staples 2003). MPEs were shown to be quickly degraded in natural sediments (Otton et al. 2008).

Studies have demonstrated that phthalates with shorter side-chains can be readily biodegraded and mineralized, whereas phthalates with longer side-chains tend to be somewhat less biodegradable (Wang et al. 2000; Chang et al. 2004; Zeng et al. 2004; Lertsirisopon et al. 2006; Liang et al. 2008). The differences in biodegradability among phthalates are attributed to the steric effects of the side-chains, where binding of hydrolytic enzymes can become hindered, resulting in limited hydrolysis. Differences in phthalate isomers can also influence rates of degradation, as phthalate-hydrolyzing enzymes are structurally specific (Liang et al. 2008).

The short-chain phthalate DMP has a long modelled half-life in air. Its measured concentrations in biota in Hudson's Bay and in air and water of the Norwegian Arctic indicate that it has some potential for long-range transport (Morin 2003). Medium- and long-chain phthalates are not persistent in air, and modelling results suggest that they are unlikely to have the potential for long-range transport (see Environment Canada, Health Canada 2015a,b,c,d), although DEHP, DBP, DIBP, DnBP, and DINP and the short-chain phthalate DEP can be associated with fine particles in areas close to emission sources (Ma et al. 2014; Ruzicková et al. 2016). DIBP was also found in biota in the Arctic (Morin 2003). Fine particle transport is considered a plausible explanation for the observed presence of DMP and DIBP in remote areas.

Phthalates have been detected in fresh water worldwide and tend to adsorb to sediments (Chang et al. 2005). In surface water, most phthalates are readily biodegradable (Furtmann 1994). In sediments, both aerobic and anaerobic microorganisms can degrade phthalates (Hashizume et al. 2002; Chang et al. 2004; Kim et al. 2008). However, despite their inherent biodegradability, phthalates can exhibit long half-lives in sediments because of the high degree of sorption driven by their hydrophobicity (Kickham et al. 2012). In aerobic biodegradation studies conducted according to the Organisation for Economic Cooperation and Development (OECD) guidelines and where wastewater treatment system sludge is used as substrate, phthalates were found to be both inherently and readily biodegradable (Environment Canada, Health Canada 2015a,b,c,d). The apparent variability in test results can be attributed to the differences in experimental protocols, concentrations of the test substance, and the substrate.

In soil, the patterns for biodegradation rates are generally very similar to those in water (Peterson and Staples 2003). Environmental conditions, such as temperature, soil moisture and oxygen levels, as well as initial substance concentrations and soil type, all have an impact on the biodegradation rate (Peterson and Staples 2003; Madsen et al. 1999; Scheunert et al. 1987). For example, half-lives for DEHP in different types of soil ranged from 2 days in loam soil to 69.3 days in sand (Rüdel et al. 1993; Shanker et al.

1985; Roslev et al. 1998; Peterson and Staples 2003) and were up to 77 days in bioremediated soil from an industrial site in Brazil (Ferreira and Morita 2012).

7.3 Potential for bioaccumulation

Bioaccumulation data for the substances in the Phthalate Substance Grouping and certain additional phthalates that were used for read-across (i.e., BBP and DEHP) are provided in the SOS reports (Environment Canada, Health Canada 2015a,b,c,d). Bioaccumulation data for other additional phthalates or obtained after the SOS reports were published are in agreement with the data presented in the SOS reports and are summarized in ECCC (2016).

Phthalates are bioavailable in the environment and certain phthalates have been measured in biota. The experimental and modelled bioaccumulation data and measurements of phthalate metabolites in aquatic organisms suggest that phthalates are effectively metabolized and thus do not tend to significantly bioaccumulate. Measured bioconcentration factors (BCFs) and bioaccumulation factors (BAFs) for aquatic species range from as low as 1 to over 3000 L/kg, with the majority of the reported values below 1000 L/kg. Biotransformation rates were found to be in the range of less than 1 to 3.5 day⁻¹. Data for sediment- and soil-dwelling organisms were also available for some phthalates and indicated that bioaccumulation in these media is not significant. Field studies confirm that phthalates do not biomagnify in the food chain (summarized in Environment Canada, Health Canada 2015a,,b,c,d).

8. Potential to cause ecological harm

8.1 Ecological effects assessment

Detailed summaries of the available effects studies for substances in the Phthalate Substance Grouping and for a number of additional phthalates and the related critical body residue calculations are presented in the SOS reports (Environment Canada, Health Canada 2015a,b,c,d), and results of additional studies, including those newly available, are tabulated in ECCC (2016). Results from toxicity studies on rodents considered as surrogates for piscivorous mammals, such as mink and otters, are presented in Health Canada (2015) and in the Human Health Effects section of this screening assessment. An analysis of the overall ecological effects dataset for phthalates, observations related to their modes of action, and key ecological effects are summarized below. Emphasis is placed on aquatic organisms, given that water is considered to be the key receiving environmental compartment of phthalates. Data on both freshwater and marine organisms are considered collectively, with no distinction made between them, as there is no reason to suspect that one or the other would have greater sensitivity to phthalates.

At acute exposure levels, phthalates have been shown to act through diester toxicity, which is a non-specific mode of action similar to baseline (non-polar) narcosis and polar narcosis, but resulting in slightly higher toxicity (Veith and Broderius 1987; Veith and Broderius 1990; Adams et al. 1995). The body of data shows that under longer-term exposures many phthalates also act through specific modes of action (MoAs). These MoAs are well documented in mammalian studies for the medium-chain phthalates, notably androgen-dependent effects affecting development of the male reproductive tract (reviewed in Health Canada 2015). In aquatic organisms, studies with exposures to phthalates of lower chain lengths, i.e., the short- and a number of medium-chain phthalates, show an array of apical and non-apical effects. Non-apical effects have been linked to estrogen and thyroid-mediated cellular pathways; however, the androgen-dependent responses have not been extensively studied in non-mammalian organisms. Non-apical responses implicated in development, reproduction, and cellular stress have been identified for certain short- and medium-chain phthalates, as well as the long-chain phthalate DnOP (Mathieu-Denoncourt et al. 2015). It is noted that for certain well-studied phthalates (e.g., BBP, DBP, DEHP) there is often variability or inconsistency among studies and model results in the observed effects or responses, such as changes in vitellogenin (VTG) levels or model estimates of receptor binding affinities. While this is likely due to the differences in design of assays and studies, it makes it a challenge to elucidate the precise MoA(s) underlying the observed effects.

8.1.1 Toxicity to aquatic organisms

Water solubility and log K_{ow} are important parameters that affect bioavailability of a substance in environmental media, thereby influencing its toxicity. Substances with very low water solubilities are likely to be less bioavailable in the environment through direct water uptake, with more likely exposure through the diet. Log K_{ow} can be an important

parameter in predicting acute toxicity for many MoAs, e.g., non-polar narcosis, polar narcosis, ester narcosis, but not for others characterized by reactive mechanisms, including electrophile MoAs. Interestingly, log K_{ow} was also observed to correlate with a receptor-based MoA, i.e., estrogen receptor (ER) binding affinity. For a series of industrial chemicals including phthalates, the binding affinity to rainbow trout ER was found to increase linearly with log K_{ow} values in the range of 1.6 to 4.6 (DMP to DBP and BBP) and to remain nearly constant at greater lipophilicity, as seen for DnHP with a log K_{ow} of 6.6 (Hornung et al. 2014). Phthalates with higher log K_{ow} (e.g., DEHP, DnOP) did not bind to the ER. For long-chain phthalates, which are characterized by very low water solubilities and high log K_{ow} values, diester toxicity seems to be the prevalent acute mode of action. It has been suggested that phthalates with alkyl chains of six or more carbons do not cause intrinsic toxicity to aquatic organisms as the rapid metabolism and low water solubility prevent the critical toxicity body burden from being reached (Bradlee and Thomas 2003). Indeed, for many of the phthalates with carbon backbones of 8 or more carbons, no acute effects have been observed below solubility limits, and the calculated tissue residues were low, not exceeding thresholds for lethal effects (see Table 8-3). However, for the poorly soluble medium-chain phthalates with backbones of 6 or 7 carbons, e.g., DEHP and B79P, high toxicities have been noted (summarized in Environment Canada, Health Canada 2015b; ECCC 2016).

An analysis of the available effects data for aquatic organisms was conducted for each phthalate. A simplified schematic is presented in Table 8-1, where data availability is noted for each substance from *in vivo* standard testing and studies characterizing effects linked to estrogen-, androgen-, and the thyroid-mediated pathways either *in vivo* or *in vitro*. *In silico* tools, including ER Expert System (ERES) (version 3) [Schmieder et al. 2014; personal communication, external peer review by US EPA, Office of Research and Development, National Health and Environmental Effects Research Laboratory Mid-Continent Ecology Division, April 2016 (ERES binding predictions 4-20-16 Excel spreadsheet), unreferenced] and TIMES (2014) have also been used to identify receptor binding potential of phthalates. *In silico*-determined binding potential of phthalates is presented in Table 8-2 for rainbow trout ER (from ERES version 3) and rodent ER (including both parent compounds and their metabolites) and androgen (AR) receptor (TIMES 2014). According to the TIMES (2014) model, metabolites of certain long-chain phthalates showed affinity for the ER, while their parent compounds were predicted to have no binding affinity for the ER.

Large data gaps were found in ecological effects information for phthalates, even though certain phthalates, such as DEHP, BBP and DBP, have been relatively well studied. Of particular importance is the lack of studies characterizing the relative potency of phthalates across the subgroups. The few studies that look at effects in the same biological system include only a small subset of phthalates, and since different endpoints are characterized, a direct comparison is not possible. Mankidy et al. (2013) observed that DEHP was more potent than BBP, on the basis of potency as an agonist of the aryl hydrocarbon receptor (AhR), whereas Zhou et al. (2011a) established a potency order of DBP>DEP>DMP>DnOP>DEHP based on abalone metamorphosis. Another limitation found in many studies is the tendency to conduct them at exposure

concentrations that are high or that exceed water solubility limits, which makes interpretation of results complicated and results in little relevance to environmental conditions. It is noted that in the few *in vivo* studies performed at very low exposure concentrations (in the range of 10^{-4} to 10^{-3} mg/L), such as those for DEHP (Oehlmann et al. 2009; Carnevali et al. 2010; Corradetti et al. 2013), deleterious effects continue to be observed. The key data gap is the lack of aquatic effects studies for phthalates conducted at environmentally relevant exposure concentrations and within solubility limits, which characterize modes of action, particularly related to the androgen-mediated pathways, and that could be linked to population-level effects.

Table 8-1. Available empirical phthalate effects data^a for aquatic organisms

Substance (CAS RN)	Standard tests for apical effects	Estrogen-mediated pathways	Androgen-mediated pathways	Thyroid-mediated pathways
DMP	Y	Y/N	–	–
DEP	Y	Y	Y	–
DPrP	Y	Y	–	–
DIBP	–	–	–	–
DBP	Y	Y	Y	Y
CHIBP	–	–	–	–
BCHP	–	–	–	–
BBP	Y	Y	Y	Y
DCHP	Y	Y	–	Y
DnHP	–	Y	–	–
DBzP	–	–	–	–
B79P	Y	–	–	–
DMCHP	–	–	–	–
DIHepP	–	–	–	N
79P	–	–	–	–
BIOP	–	–	–	–
DIOP	–	–	–	–
DEHP	Y	Y/N	Y	–
DINP	–	N	Y	–
B84P	–	–	–	–
610P	–	–	–	–
DnOP	Y	Y/N	–	Y
D911P	–	–	–	–
D911P-2	–	–	–	–
DIDP	–	–	Y	–
DIUP	–	–	–	–
DTDP	–	–	–	–
DUP	–	–	–	–

Abbreviations: Y, data available showing effects; N, data available showing no effects; Y/N, conflicting data; – , data were not identified.

^a Some studies on phthalates were conducted at high exposure concentrations, and above the water solubility limit of the tested phthalate.

Below is a brief summary of some of the available effects data for the short-, medium-, and long-chain phthalates that describes both standard studies and those describing specific MoAs. It is meant to highlight effect levels across phthalate subgroups, as observed based on standard and non-standard testing. Available ecological effects information has been previously summarized in detail in Environment Canada, Health Canada (2015a,b,c,d), and additional and newly published studies are noted in ECCC (2016).

Table 8-2. In silico predictions of estrogen receptor (ER) and androgen receptor (AR) binding capabilities of phthalates

Substance (CAS RN)	Rainbow trout ER binding (parent) (ER Expert System v3)	Rainbow trout ER binding (metabolite) (ER Expert System v3)	Rodent ER binding (parent) (TIMES 2014)	Rodent ER binding (metabolite) (TIMES 2014)	Rodent AR binding (parent) (TIMES 2014)
DMP	Y	No metabolites predicted	N	N	N
DEP	Y	N	Y	N	N
DPrP	Y	N	N	N	Y
DIBP	Y	N	N	N	Y
DBP	Y	N	Y	N	Y
CHIBP	Y	N	n/a	n/a	n/a
BCHP	Y	N	Y	Y	n/a
BBP	Y	N	Y	N	Y
DCHP	Y	N	Y	Y	n/a
DnHP	Y	N	Y	N	N
DBzP	Y	N	Y	N	N
B79P	n/a	N	Y	N	N
DMCHP	n/a	N	Y	n/a	n/a
DIHepP	n/a	N	Y	Y	N
79P	N	N	N	N	N
BIOP	n/a	N	n/a	n/a	n/a
DIOP	N	N	Y	Y	N
DEHP	N	N	Y	Y	N
DINP	N	N	N	Y	Y
B84P	n/a	N	n/a	n/a	n/a
610P	N	N	N	N	n/a
DnOP	N	N	N	N	N
D911P	N	N	N	Y	n/a
D911P-2	N	N	N	Y	n/a
DIDP	N	N	N	N	n/a

Substance (CAS RN)	Rainbow trout ER binding (parent) (ER Expert System v3)	Rainbow trout ER binding (metabolite) (ER Expert System v3)	Rodent ER binding (parent) (TIMES 2014)	Rodent ER binding (metabolite) (TIMES 2014)	Rodent AR binding (parent) (TIMES 2014)
DIUP	N	N	N	Y	n/a
DTDP	N	N	N	N	n/a
DUP	N	N	N	Y	n/a

Abbreviations: Y, receptor binder; N, receptor non-binder; n/a, result not available or substance was outside of the model domain.

Standard toxicity testing indicates that the soluble short-chain phthalates have low acute and chronic toxicity to fish, invertebrates, and algae. For DMP and DEP, fish acute median lethal concentration (LC₅₀) values were in the range of 10 to 120 mg/L (summarized in ECCC 2016). Similarly, LC₅₀ values and median effective concentration (EC₅₀) values for effects such as immobility and changes in biomass, on mysid shrimp, daphnids and algae and malformations in tadpoles were noted at exposure concentrations generally greater than 10 mg/L (summarized in Environment Canada, Health Canada 2015a; ECCC 2016; Mathieu-Denoncourt et al. 2016). In contrast, studies with abalone suggest that this species is particularly sensitive to DMP and DEP exposure, with adverse effects established through modes of action other than narcosis. For DMP, effects on larval settlement were noted at an exposure concentration of 0.05 mg/L (Yang et al. 2009), and a no observed effect concentration (NOEC) for metamorphosis was determined as 0.02 mg/L, with a 50% reduction in metamorphosis at 0.2 mg/L (Liu et al. 2009). In terms of reproductive effects, DMP-treated abalone sperm were found to exhibit dose-dependent decreases in fertilization efficiency, morphogenesis and hatchability at exposure concentrations between 0.01 mg/L and 0.1 mg/L (Zhou et al. 2011b). At an exposure concentration of 0.2 mg/L, DEP was found to reduce metamorphosis rates, and at 2 mg/L it resulted in increased abnormality rates of abalone embryos and reduced hatching rates (Zhou et al. 2011a).

For the medium-chain phthalates, moderate to high toxicity has been observed in numerous studies with aquatic organisms (summarized in Environment Canada, Health Canada 2015b; ECCC 2016). Results indicate that those with side-chain backbones of six or fewer carbons—i.e., DBP, BBP, DCHP, DEHP and B79P—are highly hazardous to fish, invertebrates, and algae, where LC₅₀ and effects such as behavioral abnormalities in fish, reproductive effects in daphnids, and effects on biomass in algae were observed at an exposure concentration of less than 1 mg/L. Secondary effects linked to estrogenic, thyroid-, or anti-androgenic modes of action are also relatively well documented for these substances, although inconsistent responses have been observed for alteration of VTG levels in studies with BBP and DEHP. BBP was shown to displace estradiol from the hepatic estrogen receptor, to inhibit ER binding, to either alter VTG production in rainbow trout following intra-peritoneal injection (Christiansen et al. 2000) or to have no impact on VTG levels in studies with fathead minnow (Study Submission 2014d; Harries et al. 2000), to impact gonadal histology (Study Submission

2014d) and to reduce spermatogonia of fathead minnows (ECHA 2009; ECHA c2007-2015). BBP also exhibited a small but significant increase in the expression of mRNA of the androgen receptor in developing fish embryos (Mankidy et al. 2013).

Most toxicity studies for DCHP in fish, amphibians, invertebrates and algae were conducted at exposure concentrations above the substance's water solubility limit (ECHA c2007–2014b; Mathieu-Denoncourt et al. 2015; Mathieu-Denoncourt et al. 2016). Two Daphnia studies, within the water solubility limit for DCHP, showed effects at low exposure concentrations, but only with chronic exposure (21-day EC₅₀ and NOEC for loss of mobility at 0.68 and 0.18 mg/L, respectively) (ECHA c2007–2014b). For DBP, 96-hour LC₅₀s of less than 1 mg/L to 7.3 mg/L in fish were determined (Buccafusco et al. 1981; Mayer and Eilersieck 1986; CMA 1984; Hudson et al. 1981; Adams et al. 1995). DBP did not induce VTG in rainbow trout or zebrafish at concentrations up to 1 mg/L (Van den Belt et al. 2003). DBP exposure concentrations in the range of 0.005 to 0.5 mg/L in different studies increased larval mortality and teratogenicity (Ortiz-Zarragitia et al. 2006), increased activity of anti-oxidant enzymes and immune-related enzymes (Xu et al. 2013), and altered plasma 11-ketotestosterone and spiggin levels (Aoki 2010; Aoki et al. 2011). For DEHP, Carnevali et al. (2010) found a significant reduction in fecundity of female zebrafish exposed to nominal concentrations ranging from 2×10^{-5} to 0.40 mg/L. Corradetti et al. (2013) also found that exposure to DEHP at a concentration of 2×10^{-4} mg/L impaired reproduction in zebrafish by inducing a number of changes, including reduced embryo production. Histological changes in fish spermatozoa and gonads (indication of intersex) and retardation of oocyte development following exposure to DEHP have also been reported (Ye et al. 2013; Kim et al. 2002b; Norman et al. 2007). While B79P studies on fish and algae were conducted at concentrations above the substance's water solubility limit, two studies on daphnids indicate that B79P is highly toxic. An acute EC₅₀ of 0.3 mg/L and a chronic NOEC for reproduction of 0.039 mg/L were determined (ECHA c2007–2014c). It is noted that these endpoints are consistent with the modelled data for aquatic species, in the range of 0.0045 mg/L for fish to 0.05 mg/L for daphnids (summarized in Environment Canada, Health Canada 2015b). (Q)SAR modelling indicates that B79P also has ER binding potential (see Table 8-1).

No evidence of toxicity was seen in standard testing for the medium-chain phthalates with longer carbon backbones—i.e., DIHepP and B84P—or for the long-chain phthalates up to their water solubility limits (summarized in Environment Canada, Health Canada 2015b-d). However, for phthalates DIDP and DINP, results from *in vitro* laboratory testing provide preliminary indications that DIDP and DINP might influence normal endocrine activity in mammalian species by altering the production of steroid hormones in the presence of an endocrine-active substance (Mlynarčíková et al. 2007; Chen et al. 2014). In a multigenerational feeding study with Japanese medaka, effects in hepatic microsomal testosterone metabolism were observed for DINP and DIDP; however, consistent adverse effects on embryo mortality, hatching success or survival were not observed (Patyna et al. 2006). Similarly, malformation and alterations in gene expression related to androgen axis were also not observed in *Xenopus* tadpoles following exposure to DINP (de Solla and Langlois 2014). *In silico* results from the

Estrogen Receptor Expert System (ERES) model with trout ER (Schmieder et al. 2014; personal communication, external peer review by US EPA, Office of Research and Development, National Health and Environmental Effects Research Laboratory Mid-Continent Ecology Division, April 2016; unreferenced) suggest no ER binding affinity for the long-chain phthalates parent compounds (see Table 8-2).

The available aquatic effects data for the medium- and long-chain phthalates with very low water solubilities and high log K_{ow} values—i.e., DIHepP, DINP, D911P, D911P-2, DIDP, DIUP, DTDP, DUP, B84P and DIOP—were above water solubility limits. It is noted that for these substances, dietary exposure is likely the more relevant route of uptake in the environment. Therefore, for DIHepP, B84P, DINP, DIDP and DUP, tissue residues (TRs) were calculated using substance-specific bioaccumulation factors (BAFs), molecular weights and water solubilities. The TR represents the internal whole body concentration of a phthalate resulting from exposure at its limit of solubility in water, taking into account its toxicokinetics as approximated by the BAF. The calculated TR values for medium-chain phthalates ranged from 5.4×10^{-3} mmol/kg (1.96 mg/kg) for DIHepP to 0.13 mmol/kg (59.1 mg/kg) for B84P and were low for the long-chain phthalates DINP at 2.6×10^{-4} mmol/kg (0.12 mg/kg), DIDP at 1.5×10^{-5} mmol/kg (0.007 mg/kg), and DUP at 5.8×10^{-8} mmol/kg (0.000028 mg/kg). Critical body residues (CBR) associated with acutely lethal baseline narcosis in small aquatic organisms typically range from about 2 to 8 mmol/kg, while those for chronic exposures range from 0.2 to 0.8 mmol/kg (McCarty and Mackay 1993). The calculated internal concentrations for the subset of the medium-chain and long-chain phthalates indicate that these phthalates are unlikely to reach levels sufficient to cause acute or chronic lethal effects toxicity in aquatic organisms, as the CBR thresholds are not surpassed. It is noted that CBR thresholds have not been developed for other modes of action including diester toxicity, and baseline narcosis is therefore assumed for those phthalates with TR calculations. It is recognized that somewhat lower CBR thresholds may be associated with other MoA(s), and thus baseline narcosis MoA may underestimate the potential toxicity, particularly under chronic exposure. Nonetheless, an overlap between CBRs for narcosis and diester toxicity is expected; accordingly, the narcosis CBR is considered appropriate for use with phthalates.

8.1.1.1 Predicted no-effect concentrations for the aquatic compartment

When experimental data were not available, modelled and analogue data were used to select critical toxicity values for the short- and medium-chain phthalates (summarized in Environment Canada, Health Canada 2015a,b). Predicted no-effect concentrations (PNECs), obtained by dividing critical toxicity values (CTVs) by the appropriate assessment factors (AFs), were then calculated and ranged from 0.00007 mg/L (DEHP) to 0.19 mg/L (DIBP). The CTVs, AFs and calculated PNECs for each phthalate are presented in Table 8-3. When PNECs could not be derived, TR to CBR comparisons were made. PNECs for the additional phthalates, which are not being assessed, ranged from 0.003 mg/L to 0.33 mg/L and can be found in ECCC (2016).

Table 8-3. Critical toxicity values and predicted no-effect concentrations for phthalates in the aquatic compartment

Substance (CAS RN)	CTV (mg/L)	Species; Effect level	Reference	AF ^a	PNEC (mg/L) [converted to mmol/L ^b]
DMP (131-11-3)	0.01	Abalone; 1-h LOEC (fertilization rate and hatching success)	Zhou et al. 2011b	10	0.001 [5.1x10 ⁻⁶]
DIBP (84-69-5)	0.56	Daphnia; 21-d NOEC	ECHA c2007–2014a	3	0.19 [6.8x10 ⁻⁴]
CHIBP (5334-09-8)	0.018 ^c	Fathead minnow; 126-d LOEC (increase in spermatogonia)	Study Submission 2014b; EC 2009	3	0.006 [2.0x10 ⁻⁵]
BCHP (84-64-0)	0.018 ^c	Fathead minnow; 126-d LOEC (increase in spermatogonia)	Study Submission 2014b; EC 2009	3	0.006 [2.0x10 ⁻⁵]
DCHP (84-61-7)	0.181	Daphnia 21-d NOEC (loss of mobility)	ECHA c2007–2014b	3	0.06 [1.8 x10 ⁻⁴]
DBzP (523-31-9)	0.08	Fathead minnow; 96-h LC ₅₀	Geiger et al. 1985	30	0.003 [8.6 × 10 ⁻⁶]
B79P (68515-40-2)	0.039	Daphnia; 22-d NOEC (reproduction)	ECHA c2007-2014c	10	0.004 [1.1 × 10 ⁻⁵]
DMCHP (27987-25-3)	0.181	Green algae; 72-h EC ₅₀ (biomass increase)	ECHA c2007-2014b	3	0.06 [1.7 × 10 ⁻⁴]
DIHepP (71888-89-6)	No effects observed below solubility limits	–	–	–	PNEC not derived; TR for fish calculated as 5.39 × 10 ⁻³ mmol/kg
BIOP (27215-22-1)	0.032	Green algae; 96-h EC ₆₀	ECOSAR v1.0	10	0.0032 [8.7 × 10 ⁻⁶]
DEHP (117-81-7)	0.0002 ^d	Zebrafish; 21-d EC ₉₀	Corradetti et al. 2013	3	0.00007 [1.7 × 10 ⁻⁷]

Substance (CAS RN)	CTV (mg/L)	Species; Effect level	Reference	AF ^a	PNEC (mg/L) [converted to mmol/L ^b]
		(reduced embryo production)			
DINP (68515-48-0 / 28553-12-0)	No effects observed below solubility limits	–	–	–	PNEC not derived; TR for fish calculated as 2.6×10^{-4} mmol/kg
B84P (16883-83-3)	No effects observed below solubility limits	–	–	–	PNEC not derived; TR for fish calculated as 0.1 mmol/kg
DIDP (26761-40-0 / 68515-49-1)	No effects observed below solubility limits	–	–	–	PNEC not derived; TR for fish calculated as 1.5×10^{-5} mmol/kg
DUP (3648-20-2)	No effects observed below solubility limits	–	–	–	PNEC not derived; TR for fish calculated as 5.8×10^{-8} mmol/kg

Abbreviations: AF, assessment factor; TR, tissue residue; CTV, critical toxicity value; d, day; EC, effect concentration; h, hour; LOEC, lowest observed effect concentration; PNEC, predicted no-effect concentration; NOEC; no observed effect concentration; –, not applicable.

^a Assessment factors in the range of 3 to 30 were applied to the critical toxicity values, on the basis of the duration of exposure period (acute or chronic), the overall robustness of the available dataset (considering factors such as the variety and sensitivity of tested species, quality and number of endpoints), and extrapolating to inter/intra species variation, short- to long-term effects, and high- to low-level effects.

^b To facilitate comparison between PNECs and the calculated TRs, units in mg/L were converted to mmol/L (by dividing the substance's PNEC by its molecular weight).

^c This CTV is based on data for BBP; see Environment Canada, Health Canada (2015b) for read-across rationale.

^d Carnevali et al. 2010 reported a lower toxicity value for DEHP for reduced fecundity in zebrafish, but this was not used as the CTV because of the lack of appropriate statistical analysis.

8.1.2 Toxicity to sediment-dwelling organisms

Sediment toxicity data are very limited for phthalates. Data for the short-chain phthalate DEP indicate low toxicity. Data for the medium-chain phthalates DBP and DEHP also indicate low toxicity (Call et al. 2001b; Brown et al. 1996). BBP, however, was found to be highly toxic to sediment-dwelling organisms (in water exposure studies) (Call et al. 2001a). For those medium-chain phthalates where PNECs in sediment could be calculated, they ranged from 0.76 mg/kg dw (B79P) to 97.8 mg/kg dw (DMCHP), and were well below the calculated values for maximum saturation in sediment (where maximum saturation in sediment was calculated using the substance's water solubility,

organic carbon-water partition coefficient (K_{oc}), and a default value of 0.04 for Canadian sediment organic carbon content). Tissue residue calculations were done for those medium-chain phthalates where effects data were above water solubility limits or not available. The highest calculated tissue residue in sediment-dwelling organisms was for DIHepP at 0.05 mmol/kg, which indicates that internal concentrations for medium-chain phthalates are unlikely to reach levels sufficient to cause acute or chronic lethal effects. In sediment toxicity studies for the long-chain phthalates, no adverse effects were observed up to the highest concentrations tested, even including those concentrations which exceeded maximum saturation limits for the substances under the study conditions. The calculated maximum tissue residue for DIDP, for example, was 0.008 mmol/kg, which is below levels sufficient to cause acute or chronic toxicity by narcosis MoA.

8.1.3 Toxicity to soil-dwelling organisms

Limited soil toxicity studies available for some short-chain phthalates (e.g., DMP) and medium-chain phthalates (e.g., BBP) indicate that these phthalates are not highly toxic to soil-dwelling organisms (summarized in Environment Canada, Health Canada 2015a,b). For the long-chain phthalates, CBR analyses for DINP and DIDP indicated that, up to soil saturation limits, internal concentrations of these substances are unlikely to reach levels sufficient to cause adverse effects (summarized in Environment Canada, Health Canada 2015c,d).

8.1.4 Toxicity to wildlife

Exposure of wildlife to short-chain phthalates via inhalation was evaluated, as these substances have a relatively high residence time in air (summarized in Environment Canada, Health Canada 2015e). An inhalation study for rats exposed to DEP (SCCNFP 2002) was used to derive a PNEC of 49 mg/m³.

Toxicity of phthalates to wildlife via food web exposure was not assessed quantitatively. Studies on secondary poisoning of wildlife were not found in the literature. Also, as noted previously in this report, phthalates are rapidly biotransformed in vertebrates and have low bioaccumulation and biomagnification potential. Therefore, exposure through the food web is not expected to pose a concern.

8.2 Ecological exposure assessment

Certain phthalates have been measured in environmental media including air, water, sediment, soil and biota in Canada and worldwide. Measured concentrations for the Phthalate Substance Grouping were presented in the SOS reports (Environment Canada, Health Canada 2015a,b,c,d). Measured concentrations for the additional phthalates in Canadian environmental media are summarized in ECCC (2016).

Information on phthalate concentrations in wastewater in Canada was obtained through a sampling campaign carried out by ECCC's Monitoring and Surveillance Program in 2014-2016. Samples of influent and effluent of on-site wastewater treatment systems at 5 industrial facilities involved in the manufacture or use of phthalates were collected and analyzed, along with samples of influent and effluent of the off-site wastewater treatment systems (WWTS)³ to which the industrial sites direct their effluents. In addition to these 5 industrial sites and corresponding WWTS, the influents and effluents of 11 other Canadian WWTS were sampled and analyzed (personal communication; unpublished environmental surveillance data received in 2015 by Ecological Assessment Division, ECCC, from Aquatic Contaminants Research Division, ECCC; unreferenced). Detection limits ranged from 0.0001 µg/L to 20.7 µg/L for individual phthalates. Two phthalates, DIOP and CHIBP, were not detected in any effluent samples. Most removal efficiencies for on-site treatment were >50%, with half being >90% and the lowest being <6%. Most removal efficiencies for off-site treatment were >50%, with less than one tenth being >90% and the lowest being <8%.

Concentrations of the different phthalates found in the effluent of the 16 WWTS were used to calculate predicted environmental concentrations (PECs) in the receiving water near the WWTS discharge point. PECs were calculated using the following equation:

$$PEC = C_{eff}/DF$$

Where

PEC: predicted environmental concentration in the receiving water body, µg/L

C_{eff}: phthalate concentration in the WWTS effluent, µg/L

DF: receiving water dilution factor (ratio of the WWTS effluent flow to the flow of the receiving water body), dimensionless.

In the risk quotient approach,⁴ the 10th percentile flow of the receiving water body was used to calculate the DF. A 10th percentile flow is used to represent conditions during approximately the lowest flow over 30-day periods, which are equivalent to typical chronic toxicity test durations. The 30-day low flows are expected and assumed to occur consecutively (summer). The resulting environmental concentrations are then compared directly to an effects concentration. Additionally, to estimate concentrations of phthalates near the point of release (near-field), the DF was limited to 10.

³ In this assessment, the term "wastewater treatment system" refers to a system that collects domestic, commercial and/or institutional household wastewater and possibly industrial wastewater (following discharge to the sewer), typically for treatment and eventual discharge to the environment. Unless otherwise stated, the term wastewater treatment system makes no distinction of ownership or operator type (municipal, provincial, federal, indigenous, private, partnerships). Systems located at industrial operations and specifically designed to treat industrial effluents will be identified by the terms "on-site wastewater treatment systems" or "industrial wastewater treatment systems."

⁴ See section 8.3 Characterization of Ecological Risk

Taking into account the longer period of time required for phthalates to accumulate in an organism's tissues, the DF for the cumulative approach⁵ was calculated using the 50th percentile flow of the receiving water body. The 50th percentile flow is used as it is deemed to more appropriately reflect the average environmental concentrations that would lead to accumulation in the organism's tissues. The use of this longer averaging period is also considered more appropriate for cumulative effects, as the highest concentrations of phthalates (used in the cumulative approach) occur at different times and locations. Short-term releases of aggregated quantities of phthalates are not expected to occur. In the case of the cumulative approach, no limit to the DF was set because the cumulative approach is not restricted to the area (near-field) where the release occurs.

PECs for industrial users and manufacturers of phthalates that were not covered by the sampling campaign were calculated using emission factors obtained from similar industrial sites where monitoring data were available. Removal rates for on-site or off-site WWTS that were not sampled were also estimated using the monitoring data for WWTS with similar types of treatment. In these cases, PECs were calculated using the following equation:

$$PEC = (Q \times C \times E \times (1 - R)) / (N \times F \times DF)$$

Where

- PEC: predicted environmental concentration in the receiving waterbody, µg/L
- Q: total yearly quantity of substance manufactured or used at an industrial site, kg/yr-site
- C: conversion factor from kg to µg, 1×10^9 µg/kg
- E: emission factors, fraction
- R: WWTS removal rate, fraction
- N: number of annual release days, d/yr
- F: effluent flow, L/d
- DF: receiving water dilution factor (ratio of the WWTS effluent flow to the flow of the receiving water body), dimensionless.

In the risk quotient approach, the 10th percentile flow of the receiving water body was used to calculate the DF. To estimate concentrations of phthalates near the point of release (near-field), the DF was limited to 10. Taking into account the longer period of time required for phthalates to accumulate in an organism's tissues, the DF for the cumulative approach was calculated using the 50th percentile flow. Also, no limit to the DF was set because the cumulative approach is not restricted to the area (near-field) where the release occurs.

⁵ See section 8.3 Characterization of Ecological Risk

Table 8-4 shows the ranges of near-field PECs developed from the monitoring and modelling discussed above. Approximately 600 PECs have been generated this way. Of the quantities manufactured or used that were reported under the s.71 survey for 2012, 95% have been accounted for by the monitoring and modelling. The remaining 5% are small volume uses and uses that are not expected to lead to significant aquatic release. The three substances with the highest PECs were B79P (3.8 µg/L), DINP (3.4 µg/L), and DCHP (3.2 µg/L).

Table 8-4. Near-field predicted environmental concentrations for phthalates

Substance (CAS RN)	Range PECs (µg/L)	Detection limit range (µg/L)	Frequency of detection in WWTS influents ^b	Frequency of detection in WWTS effluents ^b
DMP (131-11-3)	ND–0.20	1.0×10^{-3} –0.36	54 / 93	21 / 93
DEP (84-66-2)	ND–2.9	0.42–3.1	87 / 90	24 / 90
DPrP (131-16-8)	1.0×10^{-3} –0.05	4.0×10^{-3} –0.09	62 / 90	30 / 90
DIBP (84-69-5)	ND–0.21	0.07–1.6	69 / 90	16 / 90
DBP (84-74-2)	ND–0.75	0.51–3.4	19 / 90	10 / 90
CHIBP (5334-09-8)	NA	NA	0 / 0	0 / 0
BCHP (84-64-0)	ND–0.15	3.0×10^{-3} –0.02	65 / 90	40 / 90
BBP (85-68-7)	ND–2.0	0.29–3.4	64 / 90	39 / 90
DCHP (84-61-7)	ND–3.2	4.0×10^{-3} –5.5	26 / 90	5 / 90
DnHP (84-75-3)	ND – 0.01	1.0×10^{-3} – 7.0×10^{-3}	27 / 90	26 / 90
DBzP (523-31-9)	ND – 0.02	1.0×10^{-3} –0.01	78 / 90	38 / 90
B79P (68515-40-2)	ND – 3.8	1.0×10^{-3} –19	75 / 90	50 / 90
DMCHP (27987-25-3)	ND – 0.02	1.0×10^{-4} –0.01	58 / 90	36 / 90
DIHepP (71888-89-6)	ND–0.40	9.0×10^{-3} –0.20	87 / 90	39 / 90
79P (111381-89-6)	ND– 3.0×10^{-3a}	NA	0 / 0	0 / 0
BIOP (27215-22-1)	ND–0.01	1.0×10^{-3} – 6.0×10^{-3}	86 / 90	39 / 90

Substance (CAS RN)	Range PECs (µg/L)	Detection limit range (µg/L)	Frequency of detection in WWTS influents ^b	Frequency of detection in WWTS effluents ^b
DIOP (27554-26-3)	ND–0.36	0.01–13	5 / 90	0 / 90
DEHP (117-81-7)	3.0×10^{-3a} – 1.6^a	1.3–13	83 / 90	15 / 90
DINP 68515-48-0 / 28553-12-0)	ND– 3.4^a	0.33–2.8	90 / 90	28 / 90
B84P (16883-83-3)	ND–0.10	0.02–0.11	68 / 90	25 / 90
610P (68648-93-1)	0.11^a – 0.50^a	NA	0 / 0	0 / 0
DnOP (117-84-0)	ND–0.41	0.02–0.39	85 / 90	30 / 90
D911P (68515-43-5)	0.16^a – 1.1^a	NA	0 / 0	0 / 0
D911P-2 (111381-91-0)	2.0×10^{-3a}	NA	0 / 0	0 / 0
DIDP (26761-40-0 / 68515-49-1)	ND–1.3	0.14–0.48	90 / 90	64 / 90
DIUP (85507-79-5)	ND– 0.04^a	3.0×10^{-3} –0.12	87 / 90	20 / 90
DTDP (68515-47-9)	ND– 4.0×10^{-3}	1.0×10^{-4} – 1.0×10^{-3}	76 / 90	50 / 90
DUP (3648-20-2)	1.3×10^{-4} –0.09	1.0×10^{-3} –0.10	86 / 90	22 / 90

Abbreviations: ND, not detected; NA, not analyzed; PEC, predicted environmental concentration; WWTS, wastewater treatment system.

^a Modelled PEC based on industrial emission factors and s. 71 quantities.

^b Number of samples in which the phthalate was detected, divided by the total number of samples.

An analysis of the locations where both industrial and municipal monitoring was available suggests that phthalate loading from the known industrial phthalates manufacturers or users generally accounted for less than 10% of the total phthalate loading in the off-site WWTS influents. There were only two cases (DUP and B79P) where it was possible to link the presence of phthalate in a WWTS influent to an industrial user or manufacturer. This suggests that a large part of the phthalates found in the influents of off-site WWTS may be coming from other sources, such as wastewater from residential and commercial sources, industrial sources not captured by the s. 71 survey reporting requirements, or landfill leachate.

Out of the 16 off-site WWTS that were part of the sampling campaign, 3 are receiving and treating leachate from nearby landfills. For each phthalate in each of the WWTS, a

per capita influent loading was estimated. Except for 1 phthalate (DUP), where an industrial source has been identified, it was found that the average per capita loading of phthalates for a WWTS that receives landfill leachate was 2 to 9 times higher than the average per capita loading of phthalates for a WWTS that did not receive leachate. This suggests that landfill leachate may represent a non-negligible source of phthalates in WWTS influent. However, because the total quantity of phthalates entering landfills through end-of-life products, manufactured items or other materials is not known, and because concentrations of phthalates in landfill leachate were not measured, it is not presently possible to confirm or quantify the contribution of landfill leachate as a source of phthalates to WWTSs.

8.3 Characterization of ecological risk

8.3.1 General considerations

Phthalates are released both during various industrial activities and continuously through consumer use of products and manufactured items that contain phthalates, with environmental releases occurring primarily to water via off-site wastewater treatment systems. Phthalates are not chemically bound to polymer matrices, so they can migrate slowly to the polymer surface, and then possibly enter the environment. Phthalates will biodegrade rapidly and are not expected to be recalcitrant in the environment.

Degradation may be slightly slower under anaerobic conditions, thereby increasing the duration of exposure to organisms. According to information about releases and the predicted distribution in the environment, aquatic and soil-dwelling organisms close to release sites will have the highest potential for exposure. Phthalate concentrations are expected to decrease with increasing distance from points of release; however, long-range atmospheric transport potential has been identified for the short-chain phthalate DMP (Morin 2003). There is also evidence that other phthalates are transported in the atmosphere on fine particles (Ruzicková et al. 2016).

The aquatic compartment is thought to be the key receiving environmental compartment for all phthalates. Releases to the aquatic compartment are continuous, and even the long-chain phthalates, which are highly hydrophobic, are detected in water. Distribution of phthalates between environmental media depends primarily on which medium they are emitted to and also on their water solubility and partition coefficients. Short-chain and some medium-chain phthalates are expected to reside predominantly in water, and the long-chain and other medium-chain phthalates are expected to partition to sediments and adsorb to particles. Toxicity data available for soil- and sediment-dwelling organisms indicate that effects are not likely to occur at environmentally relevant concentrations. No toxicity below solubility limits or soil/sediment saturation levels was found for long-chain phthalates and some of the larger medium-chain phthalates (e.g., DIHepP, B84P). The focus of this assessment is therefore on aquatic organisms, for which deleterious effects from phthalate exposure have been observed. Acute effects of short- and medium-chain phthalates in aquatic organisms range from high (LC₅₀ of 0.08 mg/L) to moderate (LC₅₀ of 10 mg/L).

8.3.2 Cumulative risk assessment using grouping and additional phthalates

Where similar chemicals are potentially exerting combined effects on organisms through a common mode of action (MoA), it is appropriate to consider assessing risk from the cumulative exposure, rather than considering risk from each individual substance separately. In determining whether to conduct a cumulative risk assessment (CRA), the most important consideration is whether there is co-occurrence of the substances in one or more environmental media. In the case of phthalates, there are several lines of evidence to suggest the potential for co-occurrence in the environment. These include their uses, releases, degradation processes, and presence in wastewater treatment system effluents. The selection of which CRA method to use depends on whether there is a common MoA among the substances. There is sufficient evidence that, under short-term exposures, all phthalates are acting through narcosis and can be considered together in a CRA based on concentration addition (CA).

The selection of the specific CRA method depends on what types of data are available to characterize the effect and exposure concentrations of each substance. The Sum of Internal Toxic Units method was chosen from among the various CA methods available. This approach involves summing toxic units on the basis of internal toxic units (i.e., concentrations in organism tissues), rather than on the basis of external (i.e., water) exposure concentrations of substances. This is also referred to as a CBR approach.

The sum of internal toxic units (ITU_{mix}) for a group of substances is calculated using the equation shown below. For this CRA, the internal toxic unit for each substance is estimated by multiplying its estimated concentration in water (PEC_i) by the bioaccumulation factor (BAF_i), and dividing by the critical body residue (CBR) associated with chronic lethality in aquatic organisms (0.2 mmol/kg for narcosis; McCarty and Mackay 1993), multiplying CBR_i by MW_i (the molecular weight of the substance), and finally applying an assessment factor (AF). An AF of 5 was applied because the CBR is based on lethality, so the AF is intended to extrapolate from median lethal effects to sublethal low- or no-level effects. A larger factor was not deemed necessary since the CBR is already for chronic (long-term) exposure.

$$ITU_{mix} = \sum_{i=1}^n \frac{PEC_i \times BAF_i}{CBR_i \times MW_i} \times AF$$

Further detail about CRA methods, including the Sum of Internal Toxic Units (ITU) method, are found in a separate document (Environment Canada, Health Canada 2015e).

All 28 phthalates (the 14 substances in the Phthalate Substance Grouping and 14 additional phthalates) were included in a CRA calculation. Although no effects are typically observed for the long-chain phthalates when tested individually up to their solubility limits, they are the highest volume phthalates in Canadian commerce, and

monitoring data shows that some of them are present in wastewater effluents and surface waters at high concentrations. The approach chosen (ITU method) accounts for the possibility that they might still be contributing to cumulative effects based on lethality due to the narcosis MoA. Support for this approach is provided by Mayer and Reichenberg (2006), who found that highly hydrophobic substances that do not demonstrate narcotic effects on their own could still contribute to the toxicity of complex mixtures.

For the ITU calculations, the highest PEC determined for each phthalate was used, resulting in a conservative assumption that the highest concentrations of all phthalates were co-occurring at the same site. The CBR value used (in the denominator) was 0.2 mmol/kg for chronic lethal exposures (McCarty and Mackay 1993). The results of the ITU calculations are shown in Appendix B (Table B-1). The sum of internal toxic units across the 28 phthalates, prior to application of an assessment factor, is 0.033. The highest toxic unit in the mixture is for BBP (0.02). Ten phthalates account for approximately 95% of the cumulative risk based on narcosis: BBP, D911P, DCHP, B79P, DIOP, DINP, DEHP, DBP, DEP, and DIHepP (Appendix B, Figure B-1).

When the AF of 5 is applied to the sum of ITUs, the final ITU_{mix} is 0.2 (0.033 x 5). This indicates that there is low risk from the mixture. An examination of contributions of the various phthalates to the mixture toxicity indicates that the overall toxicity is largely dominated by one substance, BBP (see Appendix B1).

8.3.3 Calculation of individual risk quotients and consideration of endocrine effects

In the SOS reports (Environment Canada, Health Canada 2015a,b,c,d), risk quotient (RQ) analyses for the aquatic medium were done for the short-chain and some of the medium-chain phthalates. For the other medium-chain and the long-chain phthalates, their low water solubility and high hydrophobicity suggest that dietary exposure will be the major route of exposure for organisms, rather than the surrounding medium. For this reason, tissue residues were calculated on the basis of bioaccumulation factors and water solubility and compared with the critical body residues (CBRs) for narcosis to estimate the potential for the substance to reach internal concentrations that are sufficiently high to cause effects through baseline narcosis. None of the individual RQ or CBR results for substances in the Phthalate Substance Grouping indicated a risk of harm to aquatic organisms through narcotic effects. It should be noted that the CBRs were conservative because they were calculated using the maximum water solubility for each substance and assumed 100% bioavailability; they would be even lower if actual environmental concentrations had been used instead of water solubility limits.

The ITU approach used in this assessment employs lethality CBRs based on data for narcotic chemicals. However, effects from specific modes of action, including endocrine activity, may occur at lower exposure levels than narcotic effects. A cumulative approach based on endocrine activity is not presently viable given the data limitations. Therefore, in addition to the cumulative risk assessment based on narcosis, risk

quotients (RQs) were also calculated, using CTVs based on endocrine effects where these data were available (see Table 8-5). Although RQs were presented for the Grouping phthalates in the SOS reports, these were recalculated for this assessment using more recent PNECs and PECs, specifically those shown in Tables 8-3 and 8-4. These results, presented in Table 8-5, indicate that there is a risk to aquatic organisms from B79P and from the additional phthalate DEHP. Risk quotients for the additional phthalates, which are not being assessed, ranged from 1.2×10^{-3} to 0.58 and can be found in ECCC (2016).

The RQ based on endocrine effects calculated for DEHP indicates potential risk to aquatic organisms. The RQ for B79P, based on limited evidence for B79P in daphnids and supported by QSAR modelling, suggests that the substance is highly hazardous and indicates potential risk to aquatic organisms.

Table 8-5. Risk quotients (RQs) for Phthalate Substance Grouping and DEHP

Substance (CAS RN)	PEC (µg/L)	PNEC (µg/L)	RQ (PEC/PNEC)
DMP (131-11-3)	0.20	1.0	0.20
DIBP (84-69-5)	0.21	190	0.001
CHIBP (5334-09-8)	not analyzed	6	NC
BCHP (84-64-0)	0.15	6	0.025
DCHP (84-61-7)	3.2	60	0.05
DBzP (523-31-9)	0.02	3.0	5.5×10^{-3}
B79P (68515-40-2)	3.8	4.0	0.95
DMCHP (27987-25-3)	0.02	60	2.6×10^{-4}
DIHepP (71888-89-6)	0.40	PNEC not derived; TR for fish calculated as 5.39×10^{-3} mmol/kg	NC
BIOP (27215-22-1)	0.01	3.2	3.5×10^{-3}
DEHP (117-81-7)	1.63	0.07	23.3

Substance (CAS RN)	PEC (µg/L)	PNEC (µg/L)	RQ (PEC/PNEC)
DINP 68515-48-0 / 28553-12-0)	3.4	PNEC not derived; TR for fish calculated as 2.6×10^{-4} mmol/kg	NC
B84P (16883-83-3)	0.10	PNEC not derived; TR for fish calculated as 0.10 mmol/kg	NC
DIDP (26761-40-0 / 68515-49-1)	1.3	PNEC not derived; TR for fish calculated as 1.5×10^{-5} mmol/kg	NC
DUP (3648-20-2)	0.09	PNEC not derived; TR for fish calculated as 5.8×10^{-8} mmol/kg	NC

Abbreviations: NC, not calculated (because no adverse effects were observed below solubility limits); PEC, predicted environmental concentration (based on dilution factor of 10 and 10th percentile flow); PNEC, predicted no-effect concentration.

8.3.4 Consideration of the lines of evidence and conclusion

Phthalates examined in this screening assessment are not persistent, although all biodegrade more slowly under low oxygen conditions, and short-chain phthalates such as DMP may remain resident in air for periods of longer than two days and may be found in areas far from the source of release. Phthalates are used in a variety of consumer, commercial and industrial applications, creating the potential for widespread release into the Canadian environment. Some phthalates, in particular DINP and the long-chain phthalates DIDP and DUP, are manufactured and/or imported in large quantities. Constant release of phthalates into the environment may result in continuous exposure for organisms residing in near-field receiving media. Phthalates are released mainly into air and water, and while all phthalates are predicted to distribute into water, only short-chain phthalates such as DMP are predicted to distribute appreciably to air. Therefore, water is the primary medium of concern for the phthalates being considered in this assessment.

Phthalates are bioavailable but do not have high bioaccumulation potential because of high rates of biotransformation in biota. Long-chain phthalates demonstrate low toxicity to aquatic organisms, while short- and medium-chain phthalates exhibit moderate to high toxicity. Phthalates are efficiently metabolized, with the formation of less toxic metabolites that can be readily excreted. Narcosis is an important mode of toxic action for phthalates. However, there is strong evidence that some phthalates may also elicit effects through other modes of action. In particular, some phthalates may have the ability to adversely affect the normal functioning of endocrine systems, such as gonadal development, in organisms. While *in vivo* evidence of effects on the endocrine system has only been definitively demonstrated for a small number of phthalates, such as DEHP, an analysis of *in vivo*, *in vitro*, and *in silico* data suggests that many phthalates possess properties that could allow them to adversely influence endocrine activity under some conditions. There are considerable *in vivo* data for medium-chain phthalates in

mammals indicating endocrine effects on the development of the male reproductive tract. Given that pathways are highly conserved within vertebrates, it might be expected that, if tested, many of the data-poor medium-chain phthalates could also show effects on endocrine systems in aquatic species, such as fish.

An analysis of risk quotients determined that one phthalate included in the Phthalate Substance Grouping, B79P, and one additional phthalate, DEHP, have the potential to cause harm to aquatic organisms in Canada. Risk quotients for the remaining phthalates indicate low to moderate potential for risk to aquatic organisms in Canada.

Key lines of evidence presented in this draft screening assessment included hazardous properties of phthalates, where observed effects on aquatic organisms such as lethality and disturbances of reproduction and development can occur at low exposure levels, their continual releases and presence in the environment, and exposure analyses and the resulting risk quotients. On the basis of these lines of evidence and precaution, two phthalates, DEHP and B79P, are considered to have potential to cause ecological harm in Canada and are proposed to meet the criteria under section 64(a) of CEPA. DEHP was assessed by Environment Canada and Health Canada in 1994 under the Priority Substances Assessment Program. The assessment concluded that DEHP posed a risk to human health in Canada, but was not able to conclude on the potential for risk to the environment due to insufficient information. Sufficient data were gathered in the course of this assessment to now conclude on the potential for DEHP to cause ecological harm in Canada.

In addition to DEHP and B79P, certain short- and medium-chain phthalates (i.e., DMP, DEP, DPrP, DIBP, BCHP, DCHP, DBzP, DMCHP, BIOP, DBP, BBP, DnHP, and DINP), as well as the long-chain phthalate DnOP, may be highly hazardous because of their potential for effects on the endocrine system. However, under current exposure levels, these substances are not expected to pose a risk. The remaining phthalates in the grouping, primarily the long-chain phthalates, are considered to have low potential to cause ecological harm in Canada. The other 13 additional phthalates were only considered for purposes of informing the CRA and were not assessed as individual substances; therefore, no conclusion is made about the ecological harm of the individual additional phthalates.

8.3.5 Uncertainties in evaluation of ecological risk

Key uncertainties and a qualitative analysis of weight of evidence are presented in Table 8-6. This qualitative analysis served to determine the overall confidence in the decision-making process that led to the proposed assessment conclusion. The level of uncertainty was judged on the basis of the abundance, quality and suitability of data. The analysis also included consideration of the relevance of each line of evidence and the qualitative assessment of the weight for each line of evidence to determine their impact on the overall conclusion. Qualifiers used in the analysis ranged from low to high.

The nature and extent of the potential for phthalates evaluated in this assessment to cause adverse effects on the endocrine system in aquatic organisms is a key uncertainty. Effects on endocrine systems have been extensively studied for a few phthalates, but large data gaps remain for the majority of them. Additionally, there are inconsistent/variable study methodologies and sometimes conflicting results. Certain longer chain phthalates (>C7) may have some minor endocrine activity, or might enhance the activity of other endocrine-active substances, but the evidence does not seem to indicate that this is a significant effect for these phthalates. Consequently, while an analysis of data for endocrine activities (see Tables 8-1 and 8-2) suggests that many phthalates can potentially influence endocrine activity, the results were not sufficient to support a conclusion, under section 64 of CEPA, for all phthalates under assessment. However, phthalates with evidence for endocrine activity will be flagged for further evaluation in the event of a change to exposure conditions (for example, through increased use quantities) or receipt of additional toxicity information.

The lack of *in vivo* aquatic toxicity data on effects in endocrine systems is also an important uncertainty in the assessment. These data are not available for many of the phthalates examined in this assessment and would be particularly useful for the medium-chain phthalates as substances in this subgrouping exhibit the highest aquatic toxicity and are therefore expected to be more reactive than the short- and long-chain phthalates. Also, for those phthalates that have been tested for effects to the endocrine system, there is often a lack of testing at low, environmentally relevant concentrations. Therefore, although research is ongoing, it is currently unknown whether they might still cause adverse effects at concentrations found in the environment.

There are very limited empirical effects data of phthalates for soil- and sediment-dwelling organisms. Measurements of phthalates in soils and sediments have also been limited. Although available data suggest low concern for these environmental media, a more robust dataset would help characterize effects in these media more clearly.

There is uncertainty with respect to the sources of phthalates in the aquatic environment. For DEHP, modelling suggests that aquatic releases from industrial users (i.e., plastic products manufacturers) may be a potential source. Furthermore, considering the measured concentrations of phthalates in WWTS that receive both domestic and industrial wastewaters, the contribution of industrial activities may not be the main source of phthalates in most cases. Rather, the main sources are potentially linked to contribution from consumer or commercial inputs or landfill leachate, but it is not possible to specifically attribute the sources.

Table 8-6. Summary of lines of evidence and levels of uncertainty

Line of evidence	Level of uncertainty^a	Relevance in assessment^b	Weight assigned^c
Wide use in products, so potential for continuous release and exposure.	Moderate	Moderate	Moderate
Appropriate environmental media of distribution have been considered.	Low	Moderate	Moderate

Line of evidence	Level of uncertainty ^a	Relevance in assessment ^b	Weight assigned ^c
Overall persistence considered. Generally not persistent although DMP may remain longer than 2 days in air.	Low	High	High
Short-chain phthalates (e.g., DMP) distribute to and may persist in air; limited rodent inhalation data suggests low toxicity.	Moderate	Low	Low
Most demonstrate low bioaccumulation potential, although moderate potential in some medium-chain phthalates and all are bioavailable.	Low	High	High
Short-chain phthalates and long-chain phthalates show low toxicity by narcosis. Medium-chain phthalates have moderate to high toxicity.	Low	High	High
CBR analyses for long-chain phthalates and some medium-chain phthalates indicate tissue levels unlikely to reach those sufficient to cause adverse effects through narcosis.	Low	High	High
Evidence of rapid and efficient metabolism of phthalates in organisms, with formation of less toxic metabolites.	Low	High	High
Strong evidence of adverse effects on endocrine systems for some (e.g. DEHP); analysis of <i>in vitro</i> , <i>in vivo</i> and <i>in silico</i> data suggests many have potential to affect endocrine systems.	Moderate	High	High
Secondary poisoning: not considered because phthalates have low persistence and bioaccumulation.	High	Moderate	Low
Risk quotients indicate risk to aquatic organisms from DEHP and B79P.	Low	High	High
Risk quotient for DMP indicates potential risk to aquatic organisms.	Moderate	Moderate	Moderate
Cumulative risk analysis indicates low potential for cumulative risk through narcotic mode of action (sum of ITUs =0.2). There is uncertainty with the AF used because it is not specifically derived for a CRA analysis using ITUs.	Moderate	High	High

^a Level of uncertainty is determined on the basis of data quality, data variability, and data gaps and of whether the data are fit for purpose.

^b Relevance refers to the impact of the evidence in the assessment scientifically and/or from a regulatory perspective.

^c Weight is assigned to each line of evidence and it is directly related to its relevance in the assessment as well as factors such as data suitability and quality.

9. Potential to cause harm to human health

9.1 Exposure assessment

9.1.1 Short-chain phthalates

DMP

Exposure estimates were calculated using human biomonitoring data as well as data on DMP occurrence in indoor air, soil, dust, food and cosmetics. They are presented in the SCP SOS report (Environment Canada, Health Canada 2015a) and summarized below. Since the publication of the SOS report, DMP has been analyzed in foods included in the 2013 Canadian Total Diet Study (TDS). While it was not quantified in any food composites above the method detection limit in Canada (average MDL=1.13 ng/g; Cao et al. 2015), it was reported in indoor air in homes in the United States (Tran and Kannan 2015), in agricultural soils in Canada (Khosravi and Price 2015) and in various studies internationally. However, these reported values did not change the previously presented exposure estimates derived using environmental media and food data (Environment Canada, Health Canada 2015a).

The highest exposed group according to biomonitoring data (all sources, Maternal Infant Research on Environmental Chemicals – Child Development Plus study [MIREC-CD Plus]) are male children aged 2 to 3 years, with median and 95th percentile intakes of 0.19 and 0.66 µg/kg bw/day, respectively. For older populations (3 years and over) the highest exposed group (all sources, National Health and Nutrition Examination Survey [NHANES]) is males aged 12 to 19 years, with median and 95th percentile intakes of 0.042 and 0.29 µg/kg bw/day, respectively.

The subpopulation with the highest exposure to DMP from environmental media and food consisted of breastfed infants, with total daily intake of 0.019 and 0.26 µg/kg bw/day estimated on the basis of central tendency and upper-bounding concentrations, respectively.

Estimated daily intake of DMP from use of diaper cream (infants aged 0 to 0.5 years, dermal) was 2.7 µg/kg bw/day (lower-end exposure scenario) and 8.2 µg/kg bw/day (upper-bounding exposure scenario). For adults aged 20 years and over, estimated intakes from the use of hairsprays and hair dyes were 6.6 µg/kg bw/day (lower end) and

20 µg/kg bw/day (upper bound) and 140 µg/kg bw/event (lower end) and 420 (upper bound) µg/kg bw/event, respectively.⁶

For more details, please refer to the SCP SOS report (Environment Canada, Health Canada 2015a).

9.1.2 Medium-chain phthalates and additional phthalates

Medium-chain phthalates

For detailed information on all 10 medium-chain phthalates in this section, please refer to the MCP SOS report (Environment Canada, Health Canada 2015b).

DIBP

Exposure estimates were calculated using biomonitoring data as well as data on DIBP occurrence in air, drinking water, dust, food, plastic items and cosmetics. They are presented in the MCP SOS report (Environment Canada, Health Canada 2015b) and summarized below. Since the publication of the SOS report, DIBP has been analyzed in foods included in the 2013 Canadian TDS. DIBP was detected in 27 of 159 composite food samples at an average MDL of 7.25 ng/g (mean of positives = 8.26 ng/g, range of 2.41 to 39.8 ng/g; Cao et al. 2015). DIBP has also been detected in indoor air in homes in the United States (Tran and Kannan 2015) and in various studies internationally. However, these reported values did not significantly change the previously presented exposure estimates derived using biomonitoring and environmental media data (Environment Canada, Health Canada 2015b).

The highest exposed group according to biomonitoring data (all sources, Canadian Health Measures Survey [CHMS]) is male children aged 6 to 11 years, with estimated mean intakes of 1.5 µg/kg bw/day and median and 95th percentile intakes of 0.76 and 5.3 µg/kg bw/day, respectively. For older populations (12 years and over), the highest exposed group (all sources, CHMS) is 20-to-49-year-old females, with mean intakes of 0.56 µg/kg bw/day and median and 95th percentile intakes of 0.46 and 1.4 µg/kg bw/day, respectively.

The subpopulation with the highest exposure from environmental media and food consisted of breastfed infants, with total daily intakes of 1.6 and 5.9 µg/kg bw/day estimated on the basis of central tendency and upper-bounding concentrations, respectively. Daily intakes for DIBP for infants (0 to 1.5 years) from exposure from mouthing plastic toys and childcare articles were estimated at 62.8 and 251 µg/kg

⁶ 10% dermal absorption factor was used for all products except diaper creams (see approach for characterizing dermal absorption for DMP in SCP SOS report (Environment Canada, Health Canada 2015a).

bw/day on the basis of lower-end and upper-bounding exposure scenarios, respectively. Estimated daily intakes for infants from dermal exposure to plastic items, based on a lower-end and upper-bounding exposure scenarios, were 30.7 and 245.3 µg/kg bw/day, respectively. For adults exposed to plastic items (females aged 20 years and over), estimated daily intakes, based on lower-end and upper-bounding exposure scenarios, were 30.8 and 96.3 µg/kg bw/day, respectively. Estimated daily intake of DIBP from use of body lotions was 0.03 µg/kg bw/day for adults aged 20 to 59 years.

DCHP

Exposure estimates were calculated using data on DCHP occurrence in dust and food. Since the publication of the MCP SOS report, DCHP has been analyzed in foods included in the 2013 Canadian TDS but was detected in only 1 of 159 composite food samples, at a concentration of 64.9 ng/g (average MDL=1.58 ng/g; Cao et al. 2015). However, this new information did not significantly change the exposure estimates presented previously (Environment Canada, Health Canada 2015b).

The subpopulation with the highest exposure from environmental media and food consisted of children (aged 6 months to 4 years), with total daily intakes of 0.0018 and 0.15 µg/kg bw/day estimated on the basis of central tendency and upper-bounding concentrations, respectively. For populations aged 12 years and over, the highest exposed group is adolescents (aged 12 to 19 years), with total daily intakes of <0.001 and 0.065 µg/kg bw/day estimated on the basis of central tendency and upper-bounding concentrations, respectively.

Intakes were not calculated on the basis of biomonitoring data, because the majority of samples were measured below the limit of detection (CHMS, MIREC-CD Plus, Maternal Infant Research on Environmental Chemicals study [MIREC], Plastics and Personal Care Product Use in Pregnancy survey [P4]).

DMCHP

Exposure estimates were calculated using data on DMCHP occurrence in dust. They are presented in the MCP SOS report (Environment Canada, Health Canada 2015b) and summarized below.

The subpopulation with the highest exposure from dust consisted of infants (0 to 6 months old) with total daily intake of 0.0027 and 0.054 µg/kg bw/day estimated on the basis of central tendency and upper-bounding concentrations, respectively. For populations aged 12 years and over, total daily intakes are <0.001 µg/kg bw/day.

DBzP

Exposure estimates were calculated using data on DBzP occurrence in dust. Since the publication of the MCP SOS report, DBzP has been analyzed in foods included in the 2013 Canadian TDS and was not quantified above the MDL (average MDL=12.7; Cao

et al. 2015). Exposure estimates for DBzP are presented in the MCP SOS report (Environment Canada, Health Canada 2015b) and summarized below.

The subpopulation with the highest exposure from dust consisted of infants (0 to 6 months old), with total daily intakes of 0.016 and 0.097 µg/kg bw/day estimated on the basis of central tendency and upper-bounding concentrations, respectively. For populations aged 12 years and over, total daily intakes of <0.001 and 0.0011 µg/kg bw/day estimated on the basis of central tendency and upper-bounding concentrations, respectively, are observed for all age groups.

B84P

Exposure estimates were calculated using data on B84P occurrence in dust and plastic items. They are presented in the MCP SOS report (Environment Canada, Health Canada 2015b) and summarized below.

The subpopulation with the highest exposure from dust⁷ consisted of infants (0 to 6 months old), with total daily intakes of 0.0063 and 0.047 µg/kg bw/day estimated on the basis of central tendency and upper-bounding concentrations, respectively.

Estimated daily intakes for infants from dermal exposure to B84P from plastic items, calculated on the basis of lower-end and upper-bounding exposure scenarios, were 2.7 and 21.6 µg/kg bw/day, respectively. For adults exposed to plastic items (females aged 20 years and older), lower-end and upper-bounding estimates of daily intake were 2.7 and 8.5 µg/kg bw/day, respectively.

DIHeP

Exposure estimates were calculated using data on DIHeP occurrence in dust. They are presented in the MCP SOS report (Environment Canada, Health Canada 2015b) and summarized below.

The subpopulation with the highest exposure from dust consisted of infants (0 to 6 months old), with total daily intakes of 0.096 and 1.1 µg/kg bw/day estimated on the basis of central tendency and upper-bounding concentrations, respectively (for more details refer to Environment Canada, Health Canada 2015b). For populations aged 12 years and over, the highest exposed group is adolescents (aged 12 to 19 years), with total daily intakes of 0.0011 and 0.013 µg/kg bw/day estimated on the basis of central tendency and upper-bounding concentrations, respectively.

⁷ In the absence of an appropriate analytical method for measuring B84P in dust, and because similar quantities and uses were reported in Canada (Environment Canada 2014), B79P dust intakes were used as a surrogate for B84P dust exposure.

B79P

Exposure estimates were calculated using data on B79P occurrence in dust and plastic items. They are presented in the MCP SOS report (Environment Canada, Health Canada 2015b) and summarized below.

The subpopulation with the highest exposure from dust consisted of infants (0 to 6 months old), with total daily intakes of 0.0063 and 0.047 µg/kg bw/day estimated on the basis of central tendency and upper-bounding concentrations, respectively. For populations aged 12 years and over, total daily intakes are <0.001 µg/kg bw/day.

Estimated daily intakes for infants from dermal exposure to B79P from plastic items, as calculated on the basis of lower-end and upper-bounding exposure scenarios, were 2.7 and 21.6 µg/kg bw/day, respectively. For adults exposed to plastic items (females aged 20 years and over), estimated daily intakes, based on lower-end and upper-bounding exposure scenarios, were 2.7 and 8.5 µg/kg bw/day respectively.

DINP

Exposure estimates were calculated using biomonitoring data as well as data on DINP occurrence in dust, food, and plastic items. They are presented in the DINP SOS report (Environment Canada, Health Canada 2015c) and summarized below. Recently, DINP has been reported internationally in soils (Tran et al. 2015), indoor air (Blanchard et al. 2014, Takeuchi et al. 2014), settled dust (Blanchard et al. 2014; Luongo and Östman 2015) and tap water (Yang et al. 2014). However, these reported values did not change the exposure estimates presented previously.

The highest exposed group according to biomonitoring data (all sources, NHANES) is male children aged 6 to 11 years, with mean intakes of 4.6 µg/kg bw/day, and median and 95th percentile intakes of 4.2 and 25 µg/kg bw/day, respectively. For older populations (aged 12 years and over), the highest exposed group (all sources, NHANES) is 12-to-19-year-old males, with mean intakes of 3.0 µg/kg bw/day, and median and 95th percentile intakes of 2.6 and 33 µg/kg bw/day, respectively. For adults aged 20 years and over, daily intakes are 2.8 µg/kg bw/day (mean), 2.4 µg/kg bw/day (median), and 24 µg/kg bw/day (95th percentile) for males and 2.3 µg/kg bw/day (mean), 1.9 µg/kg bw/day (median), and 23 µg/kg bw/day (95th percentile) for females.

The subpopulation with the highest exposure from dust and food consisted of children (aged 6 months to 4 years), with total daily intakes of 1.8 and 19.7 µg/kg bw/day estimated on the basis of central tendency and upper-bounding concentrations, respectively. For populations aged 12 years and over, the highest exposed group is adolescents (aged 12 to 19 years), with total daily intakes of 1.0 and 11.4 µg/kg bw/day estimated on the basis of central tendency and upper-bounding concentrations, respectively.

Daily intakes for DINP for infants (aged 0 to 1.5 years) from mouthing plastic toys and childcare articles, were estimated on the basis of lower-end and upper-bounding exposure scenarios, to be 30 and 120 µg/kg bw/day, respectively. Estimated daily intakes for infants from dermal exposure to plastic items, based on lower-end and upper-bounding exposure scenarios, were 1.1 and 8.6 µg/kg bw/day, respectively. For females aged 20 years and over, estimated daily intakes from dermal exposure to plastic items, based on lower-end and upper-bounding exposure scenarios, were 1.1 and 3.4 µg/kg bw/day, respectively.

CHIBP, BCHP and BIOP

Given the absence of reporting to the s. 71 industry survey (CHIBP, BCHP and BIOP), non-detection in dust (CHIBP and BCHP), non-detection in products used by consumers (BCHP; emission chamber study, NRC 2012), negligible modelled indoor air concentrations (CHIBP), and the absence of information as to their presence in product databases (CHIBP, BCHP and BIOP), general population exposure to CHIBP, BCHP and BIOP from environmental media and products used by consumers is expected to be negligible (Environment Canada, Health Canada 2015b).

Additional medium-chain phthalates

BBP

Biomonitoring

Monobenzylphthalate (MBzP), the main monoester metabolite of BBP, was monitored in the CHMS Cycle 1 (2007–2009) and Cycle 2 (2009–2011), with 100% detection in all samples (Health Canada 2011b, 2013). Additionally, MBzP was measured as part of the First Nations Biomonitoring Initiative (FNBI) of the Assembly of First Nations (n=492 for on-reserve and Crown-land populations aged 20 years and over). Urine concentrations for MBzP (geometric mean) were reported to be statistically higher in FNBI samples than those observed in the CHMS population (AFN 2013).

MBzP was also monitored by Health Canada in three cohort surveys: P4 (n = 31 women and their infants, 542 individual spot samples, women provided multiple urine samples over two visits), MIREC (n = 1742 pregnant women, spot urine samples), and MIREC-CD Plus (197 children aged 2 to 3 years, 1 spot sample per individual). All three surveys reported high detection frequencies of MBzP (100%, 99% and 97%, respectively) (personal communication from Environmental Health Sciences and Radiation Directorate [EHSRD], Health Canada, to Existing Substances Risk Assessment Bureau [ESRAB], Health Canada, October 2013, 2014, unreferenced; Arbuckle et al. 2014).

Finally, in the United States, the NHANES also monitored MBzP in urine during survey years 1999 to 2012 and reported high detection frequencies (CDC 2014).

Using the CHMS, P4, MIREC and MIREC-CD Plus datasets, reverse dosimetry intake estimates were generated. Metabolite concentrations were adjusted for urine dilution using the creatinine correction method, a commonly used method for phthalate biomonitoring assessment (Fromme 2007; Frederiksen et al. 2013; Christensen et al. 2014; US CPSC CHAP 2014). Daily creatinine excretion rates for participants were estimated using the Mage equation. Biomonitoring intakes are presented in Table 9-1 below (see Appendix C for further information on the methodology).

Table 9-1. Biomonitoring daily intakes ($\mu\text{g}/\text{kg bw}/\text{day}$) for BBP^a

Age group	Study	Male/ Female	n	Arithmetic mean	50th	75th	95th ^h
1–4 months	P4	males and females	48	0.607	0.253	0.513	1.802
2–3 years	MIREC-CD Plus	males and females	198	0.873	0.379	0.853	2.97
3–5 years	CHMS	males and females	519	1.4	0.76	1.6	4.5
6–11 years	CHMS	males	261	1.2	0.79	1.6	3.4
6–11 years	CHMS	females	253	0.93	0.61	1.1	2.7
12–19 years	CHMS	males	255	0.53	0.36	0.59	1.4
12–19 years	CHMS	females	255	0.46	0.28	0.53	1.6
18+ years	MIREC	females (pregnant)	1727	0.53	0.27	0.53	1.60
19+ years	P4	females (pregnant)	31 ^c	1.0	0.31	0.86	3.01
20–49 years	CHMS	males	290	0.33	0.2	0.35	0.97 ^b
20–49 years	CHMS	females	286	0.37	0.19 ^b	0.36 ^b	1.2
50–79 years	CHMS	males	211	0.22	0.13	0.23	0.61 ^b
50–79 years	CHMS	females	216	0.24	0.15	0.3	-

- = No data

^a Data for males and females from: P4 and MIREC pregnant women, P4 infants, MIREC-CD Plus children (preliminary results), and CHMS (Cycle 2)

^b Use data with caution.

^c n = 31 women, 542 individual spot samples, women provided multiple urine samples over two visits.

The highest exposed group according to biomonitoring data (all sources, CHMS) is children aged 3 to 5 years with median and 95th percentile intakes of 0.76 and 4.5 $\mu\text{g}/\text{kg bw}/\text{day}$, respectively. For older populations, the highest exposed group (all

sources, P4) is pregnant women (aged 19 years and over) with median and 95th percentile intakes of 0.31 and 3.01 µg/kg bw/day, respectively.

Environmental media and food

The subpopulation with the highest exposure to BBP from environmental media and food consisted of children (aged 0.5 to 4 years), with total daily intakes of 0.58 and 2.99 µg/kg bw/day estimated on the basis of central tendency and upper-bounding concentrations, respectively (Appendix D, Table D-1a).

Indoor air and dust

One study measured BBP in indoor air in Canadian homes; all samples were less than the limit of detection (LOD) (LOD was not reported; Zhu et al. 2007). Recently, BBP has also been measured in indoor air in homes in the United States (detected in 100% of 20 samples from homes in Albany, NY, method quantification limit = 0.20 ng/m³, median: 2.99 ng/m³, maximum: 24.7 ng/m³; Tran and Kannan 2015) and internationally (Fromme et al. 2004; Rudel et al. 2010; Bergh et al. 2011a; Pei et al. 2013; Blanchard et al. 2014; Lin et al. 2014; Takeuchi et al. 2014). As no Canadian indoor air survey reported BBP above the LOD, median (2.99 ng/m³) and maximum (24.7 ng/m³) concentrations from the US study (Tran and Kannan 2015) were used to estimate the general population daily intake of BBP from indoor air (Appendix D, Table D-1a).

BBP was surveyed in the Canadian House Dust Study (CHDS) and was detected in 100% of homes (range: 0.6 to 944 µg/g, median: 42.3 µg/g, 95th percentile: 512 µg/g) (Kubwabo et al. 2013). Internationally, BBP has also been reported in house dust (Fromme et al. 2004; Bornehag et al. 2005; Kolarik et al. 2008; Langer et al. 2010; Bergh et al. 2011a; Guo and Kannan 2011; Hsu et al. 2012; Kang et al. 2012; Gevao et al. 2013; Orecchio et al. 2013; Papadopoulos et al. 2013; Blanchard et al. 2014; Lin et al. 2014; Dodson et al. 2015; Luongo and Östman 2015).

BBP has applications as a plasticizer in the manufacturing of automobiles and automobile parts (ECHA 2012; Environment Canada 2014). For the general population, indirect exposure (e.g., off-gassing) is considered a relevant source, but no data on this exposure source has been identified, which is currently an uncertainty in the draft screening assessment.

The Canadian survey (Kubwabo et al. 2013) was identified as the key study for exposure characterization, and median (42.3 µg/g) and 95th percentile (512 µg/g) concentrations were used to estimate the Canadian general population daily intake of BBP from dust (Appendix D, Table D-1a).

Food, infant formula and breast milk

In Canada, BBP presence in food was measured in samples from the 2013 Canadian TDS (Cao et al. 2015). BBP was detected in 32 of 159 food composite samples

(average MDL = 3.10 ng/g), with a mean concentration of 12.4 ng/g and a range of 1.86 to 82.7 ng/g (Cao et al. 2015). Milk, soft drinks, and fruit juice are the major sources of intake for all population groups. In addition, BBP presence in food was monitored as part of the Canadian Food Inspection Agency's (CFIA) 2013-2014 and 2014-2015 Food Safety Action Plan (FSAP) surveys (personal communication from the Food Directorate, Health Canada, to ESRAB, Health Canada, April 2014; unreferenced). BBP was detected in less than 1% of 1518 (LOD: 0.1 µg/g) packaged and processed food samples at concentrations ranging from 0.3 to 1.9 µg/g, with a mean of the positive samples of 0.75 µg/g.

Additionally, breast milk was monitored as part of the MIREC study. BBP was not detected in any samples (n=305; MDL=0.00741 µg/g; personal communication from the Food Directorate, Health Canada, to ESRAB, Health Canada, October 2014; unreferenced). Internationally, BBP was detected in breast milk from one study in Sweden (Högberg et al. 2008) and not detected in another study in Germany (Fromme et al. 2011). However, BBP readily metabolizes to MBzP in the human body (Koch and Calafat 2009; Frederiksen et al. 2011), and as a result, BBP, as the parent compound, may not be found in breast milk in high quantities.

MBzP was measured in breast milk as part of the P4 study (n = 31 women, 56 breast milk samples collected from study participants). It was detected in 34% of breast milk samples, with the median value reported as below the LOD (0.018 µg/L) and the maximum value reported as 0.16 µg/L (personal communication from EHSRD, Health Canada, to ESRAB, Health Canada, October 2013; unreferenced). Internationally, MBzP has been detected in breast milk (Mortensen et al. 2005; Högberg et al. 2008).

In the P4 study, MBzP was detected in <5% of samples of infant formula (n=23; LOD=0.018 µg/L) (personal communication from EHSRD, Health Canada, to ESRAB, Health Canada, October 2013; unreferenced). The CFIA surveillance data from the 2013-2014 and 2014-2015 FSAP surveys did not detect BBP (LOD= 0.1 µg/g) in any samples of infant foods (n=44), infant formula (n=59) or infant cereals (n=19). Internationally, BBP was not detected in infant formulas in two European studies (Sørensen 2006; Bradley et al. 2013a).

Using Canadian TDS data, probabilistic estimates of dietary intakes were derived for BBP and results are outlined in Appendix D, Table D-1b (for methodology for estimating probabilistic intakes, see Appendix E). Results for BBP in breast milk and infant formula that were below the LOD (i.e., 0.018 µg/L) were set to half the LOD (Appendix D, Table D-1a).

Ambient air, drinking water and soil

No Canadian data were identified for BBP in ambient air. Rudel et al. (2010) measured outdoor air outside homes in the United States (detected in 5% of 43 samples [method reporting limit = 6 ng/m³], median: not reported, maximum: 8.5 ng/m³). Internationally, BBP has been reported in ambient air (Li and Wang 2015). Rudel et al. (2010) was

identified as the relevant study for exposure characterization (sampling from North America), and half the method reporting limit (method reporting limit [MRL] = 6 ng/m³) and maximum (8.5 ng/m³) concentrations were used to estimate potential exposures to BBP via ambient air (Appendix D, Table D-1a).

No Canadian data were identified for BBP in drinking water. BBP was analyzed for, but not detected in, Canadian bottled water (MDL: 0.085 µg/L; Cao 2008). Similarly, BBP was not detected in any samples of well water intended to be bottled in Spain (Bono-Blay et al. 2012). Internationally, BBP has been detected in bottled water (Jeddi et al. 2015, Lv et al. 2015), drinking water (Liu et al. 2015), and surface waters (Net et al. 2015, Selvaraj et al. 2015). It was not detected in any samples of tap water or river water in Spain (Dominguez-Moruco et al. 2014). In the absence of Canadian or North American data on levels of BBP in tap water, half the MDL (i.e., 0.085 µg/L) for BBP in bottled water was used to estimate the general population daily intake from drinking water (Cao et al. 2008) in Canada (Appendix D, Table D-1a).

Khosravi and Price (2015) reported various phthalates in agricultural soils in both control and biosolid amended soils collected in Nova Scotia, Canada. BBP was reported at 0.13 ng/g (control soil) and 2.4 ng/g (biosolid amended soil) (Khosravi and Price 2015). Internationally, BBP has been detected in soils (Cheng et al. 2015; Tran et al. 2015; Wang et al. 2015). Conversely, Hongjun et al. (2014) did not detect BBP in any samples of urban, suburban or rural soils in China. The reported concentration of BBP in control agricultural soils (0.13 ng/g; Khosravi and Price 2015) was used to estimate potential exposures to BBP via soil in Canada (Appendix D, Table D-1a).

Products used by consumers

Globally, BBP may also be present in a wide variety of manufactured items, including childcare articles, children's toys, do-it-yourself (DIY) products, paints and exercise balls (HPD 1993- ; ECHA 2012; Korfali et al. 2013; AGDH 2015). In Canada, BBP has also been reported as a plasticizer used in various types of manufactured items (NRC 2012; See Table 2-2; Environment Canada 2014).

Toys and childcare articles

Health Canada has surveyed soft vinyl toys and childcare articles over a number of years for multiple phthalates, including BBP, and it was detected in only one sample from the 2008 survey (below the restricted limit) and has not been detected since (Health Canada 2007, 2009, 2012, 2014). BBP was also monitored in toys purchased in Canada, but made elsewhere; it was detected at 0.001% to 0.02% (Stringer et al. 2000). Internationally, BBP was monitored in toys in India. It was detected in 3 of 24 toy samples, all at <0.1% (Johnson et al. 2011).

Currently, Canada (like the United States and the European Union) has regulations in place limiting the amount of certain phthalates (including BBP) in toys and childcare articles (*Phthalates Regulations* under the *Canada Consumer Product Safety Act*

[Canada 2016]). The European Union (EU)'s Rapid Alert System for Non-Food (RAPEX) database also shows low reporting of toys tested in violation of the regulation for BBP (RAPEX 2015), and the United States Consumer Product Safety Commission (US CPSC) recently stated that less than 10% of exposures to BBP for infants and children would result from mouthing of toys and childcare articles (US CPSC CHAP 2014).

Given the absence of BBP in toys and childcare articles reported in Canadian and international monitoring studies, exposure is expected to be negligible and oral intakes from mouthing toys and/or childcare articles were not estimated.

Cosmetics

On the basis of notifications submitted under the *Cosmetic Regulations*, BBP is not expected to be present in cosmetics in Canada (personal communication from the Consumer Product Safety Directorate [CPSD], Health Canada, to ESRAB, Health Canada, July 2015; unreferenced). Internationally, BBP has been detected in various types of cosmetics and personal care products⁸ (Guo and Kannan 2013; Guo et al. 2013; Bao et al. 2015). In contrast, Liang et al. (2013) did not detect BBP in cosmetics in China. This presence may be due to potential migration from packaging. A summary of recent studies measuring concentrations of BBP in cosmetics and personal care products reported in North America is outlined in Table 9-2.

Table 9-2. Concentrations of BBP in cosmetics and personal care products

Detection frequency and product types ^a	Concentration (µg/g)	Reference (country)
12% of 41 rinse-off products	ND–0.18	Guo and Kannan 2013 (United States)
13% of 109 leave-on products	ND–78.3	Guo and Kannan 2013 (United States)
5% of 20 baby products	ND–0.14	Guo and Kannan 2013 (United States)

^a Limits of detection: Koniacki et al. 2011 (0.1 µg/g), Guo and Kannan 2013 (0.01 µg/g)

BBP was not reported as used in Canada. The United States reported low detection frequencies (5% to 13%), and the majority of the concentrations in all studies were in the sub-ppm range. Exposure to BBP from personal care products and cosmetics is therefore not considered significant. In addition, NICNAS (AGDH 2015) and US CPSC CHAP (2014) reported that the cosmetic use of BBP is likely to be rare and they did not assess exposure from this source. For that reason, exposure estimates from this source were not generated.

⁸ For the purpose of this document, a personal care product is defined as a substance or mixture of substances, in a product, that is generally recognized by the public for use in daily cleansing or grooming. Depending on how the product is represented for sale and its composition, personal care products may fall into one of three regulatory categories in Canada, cosmetics, drugs or natural health products.

Other products used by consumers

Globally, BBP may be found in paint products (US CPSC CHAP 2014; AGDH 2015). This use has also been reported in Canada (Environment Canada 2014). The US CPSC CHAP (2014) reported that aerosol paints may contribute to >10% of exposure to BBP for adults, infants, toddlers and children.

In addition, BBP may have applications in the production of articles that may come in contact with skin (ECHA 2012; AGDH 2015). However, BBP was reported in only 1 of 35 samples of children’s clothing (Brigden et al. 2013). The US CPSC CHAP (2014) did not evaluate dermal exposure to items containing BBP.

However, since exposure to BBP from these uses is considered to be captured by the available Canadian biomonitoring data estimates of exposure were not calculated.

DBP

Biomonitoring

Mono-n-butyl phthalate (MnBP), the major monoester metabolite of DBP, was monitored in the CHMS Cycle 1 (2007-2009) and Cycle 2 (2009-2011) with 100% detection in all samples (Health Canada 2011b, 2013). Additionally, MnBP was measured as part of the First Nations Biomonitoring Initiative (n=492 for on-reserve and Crown-land populations aged 20 years and over). Urine concentrations for MnBP (geometric mean) were reported to be similar in FNBI samples to those reported in the CHMS (AFN 2013).

MnBP was also monitored by Health Canada in three cohort surveys: P4, MIREC and the MIREC-CD Plus. All three surveys reported high detection frequencies of MnBP (100%, 99% and 100%, respectively; personal communication from EHSRD, Health Canada, to ESRAB, Health Canada, October 2013, 2014, unreferenced; Arbuckle et al. 2014). An additional metabolite of DBP (MHBP) was also monitored and detected at high frequency (92% and 100%, respectively) in the P4 and MIREC-CD Plus studies (personal communication from EHSRD, Health Canada, to ESRAB, Health Canada, October 2013, 2014; unreferenced).

Using the CHMS, P4, MIREC and MIREC-CD Plus datasets, reverse dosimetry intake estimates were generated as previously described. Biomonitoring intakes are presented in Table 9-3 below (see Appendix C for further information on the methodology).

Table 9-3. Biomonitoring daily intakes (µg/kg bw/day) for DBP^a

Age group	Study	Male/ Female	n	Arithmetic mean	50th	75th	95th
1–4 months	P4	males and females	48	0.830	0.572	1.126	1.900
2–3	MIREC-	males and	192	1.19	0.939	1.39	2.71

Age group	Study	Male/ Female	n	Arithmetic mean	50th	75th	95th
years	CD Plus	females					
3–5 years	CHMS	males and females	519	2.4	1.7	2.5	5.3 ^b
6–11 years	CHMS	males	260	-	1.3	2.3 ^a	-
6–11 years	CHMS	females	253	-	1.3	2.1	5.3 ^b
12–19 years	CHMS	males	255	1.4	0.85	1.4	3.2 ^b
12–19 years	CHMS	females	255	0.84	0.71	1.1	1.8
18+ years	MIREC	females (pregnant)	1728	1.24	0.66	1.04	2.66
19+ years	P4	females (pregnant)	31 ^c	1.39	0.55	0.96	4.11
20–49 years	CHMS	males	290	0.86	0.58	0.9	1.8 ^b
20–49 years	CHMS	females	284	0.91 ^b	0.55	0.79	0.6 ^b
50–79 years	CHMS	males	210	0.6	0.43	0.67	1.5
50–79 years	CHMS	females	216	0.69	0.51	0.72	1.7 ^b

- = No data

^a Data for males and females from: P4 and MIREC pregnant women, P4 infants, MIREC-CD Plus children (preliminary results), and CHMS (Cycle 2)

^b Use data with caution

^c n = 31 women, 542 individual spot samples, women provided multiple urine samples over two visits.

The highest exposed group according to biomonitoring data (all sources, CHMS) is children aged 3 to 5 years, with median and 95th percentile intakes of 1.7 and 5.3 µg/kg bw/day, respectively. For older populations, the highest exposed group (all sources, P4) is pregnant women (aged 19 years and over), with median and 95th percentile intakes of 0.55 and 4.11 µg/kg bw/day, respectively.

Environmental media and food

The subpopulation with the highest exposure to DBP from environmental media and food consisted of children (aged 0.5 to 4 years), with total daily intakes of 0.88 and 2.96 µg/kg bw/day estimated on the basis of central tendency and upper-bounding concentrations, respectively (Appendix D, Table D-2a).

Indoor air and dust

One study measured DBP in indoor air in Canadian homes (LOD was not reported; Zhu et al. 2007). They reported air concentrations of 200 ng/m³ (median) and a range of 130 to 1100 ng/m³ (Zhu et al. 2007). Recently, DBP has also been measured in indoor air in homes in the United States (detected in 100% of 20 samples from homes in Albany, NY, method quantification limit = 0.10 ng/m³, median: 22.6 ng/m³, maximum: 111 ng/m³; Tran and Kannan 2015) and internationally (Blanchard et al. 2014; Lin et al. 2014; Takeuchi et al. 2014). The Canadian indoor air survey concentrations (median: 200 ng/m³ and maximum: 1100 ng/m³; Zhu et al. 2007) were used to estimate the general population daily intake of DBP from indoor air in Canada (Appendix D, Table D-2a).

DBP was surveyed in the CHDS and was detected in 99% of homes (range: ND–1392 µg/g, median: 16.8 µg/g, 95th percentile: 95.4 µg/g; Kubwabo et al. 2013). Internationally, DBP has also been reported in house dust (Dodson et al. 2015; Luongo and Östman 2015).

DBP has applications as a plasticizer in the manufacturing of automobiles and automobile parts (ECHA 2012; AGDH2013a). For the general population, indirect exposure (e.g., off-gassing) is considered a relevant source, but no data on this exposure source has been identified, which is currently an uncertainty in the draft screening assessment.

The Canadian survey (Kubwabo et al. 2013) was identified as the key study for exposure characterization, and median (16.8 µg/g) and 95th percentile (95.4 µg/g) concentrations were used to estimate the Canadian general population daily intake of DBP from dust (Appendix D, Table D-2a).

Food, infant formula and breast milk

In Canada, DBP presence in food was monitored in samples from the 2013 Canadian TDS (Cao et al. 2015). DBP was detected in 44 of 159 food composite samples (average MDL=16.6 ng/g) with a mean concentration of the positive samples of 23.2 ng/g and a range of 6.21 – 208 ng/g (Cao et al. 2015). Milk, soft drinks, bread, and ice cream are the major sources of intake for the overall population. In addition, DBP presence in food was monitored as part of the CFIA 2013-2014 and 2014-2015 FSAP surveys (personal communication from the Food Directorate, Health Canada, to ESRAB, Health Canada, April 2014; unreferenced). DBP was detected in 14% of 1518 (LOD: 0.1 µg/g) packaged and processed food samples. DBP concentrations ranged from 0.26 to 4.3 µg/g with a mean concentration of the positive samples of 0.76 µg/g.

MnBP was measured in breast milk as part of the P4 study (n = 31 women, 56 breast milk samples collected from study participants, LOD=0.057 µg/L). It was detected in 100% of breast milk samples, with median and maximum values reported as 0.656 and 5.18 µg/L, respectively (personal communication from EHSRD, Health Canada, to ESRAB, Health Canada, October 2013; unreferenced). Internationally, MnBP has been measured in breast milk in Europe (Fromme et al. 2011).

Breast milk was also monitored as part of the MIREC study. DBP was detected in 21 samples (n=305, median=0.0129 µg/g, range= <MDL-0.030 µg/g, MDL=0.0149 µg/g; personal communication from Food Directorate, Health Canada, to ESRAB, Health Canada, October 2014; unreferenced). Internationally, DBP was detected in breast milk from one study in Sweden (Högberg et al. 2008) and Germany (Fromme et al. 2011). However, DBP readily metabolizes to MnBP in the human body (Koch and Calafat 2009) and would therefore not be expected in breast milk in high frequency.

Recently, an analysis of 23 infant formula samples in the P4 study showed 80% detection of MnBP (LOD: 0.057 µg/L, median: 0.299 µg/L, maximum: 1.16 µg/L) (personal communication from EHSRD, Health Canada, to ESRAB, Health Canada, October 2013; unreferenced). However, measurement of this metabolite in infant formula was affected by high field blank levels (possible contamination); and therefore, was not used to quantify intakes. The CFIA surveillance data did detect DBP in 3 samples of infant foods (n=20, median: ND, 95th percentile: 0.675 µg/g), 12 samples of infant formula (n=32, median: ND, 95th percentile: 1.12 µg/g) and 4 samples of infant cereals (n=7, median: 0.42 µg/g, 95th percentile: 1.79 µg/g; personal communication from the Food Directorate, Health Canada, to ESRAB, Health Canada, April 2014; unreferenced). Internationally, DBP has been detected in infant formulas in Italy and Europe (Cirillo et al. 2015), but not in the United Kingdom (Bradley et al. 2013a).

Using TDS data, probabilistic estimates of dietary intakes for DBP were derived for the Canadian general population and results are outlined in Appendix B, Table B-2b (the methodology for estimating probabilistic intakes is provided in Appendix E). Median (0.656 µg/L) and maximum (5.18 µg/L) values of MnBP (metabolite of DBP) in breast milk measured in the P4 study was used for risk characterization (Appendix D, Table D-2a).

Ambient air, drinking water and soil

No Canadian data were identified for DBP in ambient air. Rudel et al. (2010) measured outdoor air outside homes in the United States (detected in 35% of 43 samples [MRL = 7 ng/m³], maximum: 32 ng/m³). Internationally, DBP has been reported in ambient air (Li and Wang 2015). Rudel et al. (2010) was identified as the relevant study for exposure characterization (sampling from North America), and half the MRL (7 ng/m³) and maximum (32 ng/m³) concentrations were used to estimate potential exposures to DBP via ambient air (Appendix D, Table D-2a).

No Canadian data were identified for DBP in drinking water. In Canada, Cao et al. (2008) surveyed phthalates in bottled carbonated and non-carbonated water and detected and quantified DBP in all 11 samples (range: 0.075 – 1.72 µg/L). Internationally, DBP was also detected in bottled water samples (Jeddi et al. 2015; Lv et al. 2015), surface waters (Li et al. 2015; Net et al. 2015; Selvaraj et al. 2015), and tap water (Liu et al. 2015). In the absence of Canadian and North American data on levels of DBP in tap water, mean (0.357 µg/L) and maximum (1.72 µg/L) concentrations of

DBP in bottled non-carbonated water were used to estimate the general population daily intake from drinking water (Cao et al. 2008) in Canada (Appendix D, Table D-2a).

Khosravi and Price (2015) reported various phthalates in agricultural soils in both control and biosolid amended soils collected in Nova Scotia, Canada. DBP was reported at 0.14 ng/g (control soil) and 1.1 ng/g (biosolid amended) (Khosravi and Price 2015). Internationally, DBP has been detected in soils (Cheng et al. 2015; Tran et al. 2015; Wang et al. 2015). The reported concentration of DBP in control agricultural soils (0.14 ng/g; Khosravi and Price 2015) was used to estimate potential exposures to DBP via soil in Canada (Appendix D, Table D-2a).

Products used by consumers

Globally, DBP may also be present in a wide variety of manufactured items, including childcare articles, children’s toys, DIY products, gloves and exercise balls (HPD 1993- ; Stringer et al. 2000; ECHA 2012; Chao et al. 2013; Korfali et al. 2013; AGDH 2013a). In Canada, DBP has also been reported as a plasticizer used in various types of manufactured items (NRC 2012; See Table 2-2; Environment Canada 2014).

Toys and childcare articles

Numerous studies have examined the concentrations of DBP in childcare articles and toys (Stringer et al. 2000; Biedermann-Brem et al. 2008; Johnson et al. 2011; Korfali et al. 2013). A summary of DBP reported in toys and childcare articles available in Canada are presented in Table 9-4.

Table 9-4. Percent content of DBP in various soft vinyl toys and childcare articles available in Canada

Detection frequency	Percent content	Reference
0 of 117 samples	<0.1%	Health Canada 2014 (Canada)
1 of 62 samples	>0.1%	Health Canada 2012 (Canada)
1 of 38 samples	>0.1%	Health Canada 2009 (Canada)
4 of 72 samples	>0.1%	Health Canada 2007 (Canada)

Currently, Canada (like the United States and the European Union) has regulations in place limiting the amount of certain phthalates (including DBP) in toys and childcare articles (*Phthalates Regulations* under the *Canada Consumer Product Safety Act* [Canada 2016]). The EU’s RAPEX database also shows low reporting of toys tested in violation of the regulation for DBP (RAPEX 2015), and the US CPSC recently stated that less than 10% of exposures to DBP for infants and children would result from mouthing of toys and childcare articles (US CPSC CHAP 2014).

Given the absence of DBP in toys and childcare articles reported in Canadian monitoring studies and the low frequency and low percent content of DBP reported in international monitoring studies, exposure is expected to be negligible and oral intakes from mouthing toys and/or childcare articles were not estimated.

Cosmetics

On the basis of notifications submitted under the *Cosmetic Regulations*, DBP is likely to be present in cosmetics in Canada, specifically nail polishes (personal communication from the CPSPD, Health Canada, to ESRAB, Health Canada, July 2015; unreferenced).

Koniecki et al. (2011) reported DBP in cosmetics purchased in Canada, including hair sprays, mousses, nail polishes, skin cleansers and baby shampoos. Internationally, DBP has been detected in various types of cosmetics and personal care products (Guo and Kannan 2013; Guo et al. 2013; Liang et al. 2013). A summary of recent studies measuring concentrations of DBP in cosmetics and personal care products reported in North America is outlined in Table 9-5.

Table 9-5. Concentrations of DBP in cosmetics and personal care products

Detection frequency and product types ^a	Concentration (µg/g)	Reference (country)
8% of 85 fragrance, haircare and deodorant products	ND-36	Koniecki et al. 2011 (Canada)
7% of 69 nail polish, lotion and skin cleanser products	ND-24304	Koniecki et al. 2011 (Canada)
2% of 98 baby products	ND-1.8	Koniecki et al. 2011 (Canada)
17% of 41 rinse-off products	ND-0.69	Guo and Kannan 2013 (United States)
39% of 109 leave-on products (including nail polishes)	ND-27400	Guo and Kannan 2013 (United States)
20% of 20 baby products	ND-0.22	Guo and Kannan 2013 (United States)

^a Limits of detection: Koniecki et al. 2011 (0.1 µg/g), Guo and Kannan 2013 (0.01 µg/g)

Given that the North American studies report that detection frequencies are low (2% to 8% in Canada, 17 to 39% in US) and the majority of the concentrations in all three studies are in the sub-ppm range, exposure from personal care products and cosmetics are not considered significant. The exception is nail polishes, as both North American studies showed high concentrations of DBP in nail polishes (Koniecki et al. 2011 and Guo and Kannan 2013). In addition, the US CPSC CHAP (2014) indicated that nail polish as a product type would likely contribute to >10% of exposure to DBP, and NICNAS (AGDH 2013a) reported that this type of product was most likely to contain the highest amount of DBP. Therefore, estimates of dermal exposure from nail polishes as a worst-case representative scenario are presented in Table 9-6.

Table 9-6. Estimates of dermal exposure from nail polish use^a

Product type	Concentration (µg/g)	Intake (µg/kg bw/day)
Nail polish	Mean: 5280; Max: 27400 ^b	Mean:0.16; Max: 0.83

^aApplied a 10% dermal absorption factor. See Appendix H in Environment Canada, Health Canada 2015b for approach to characterizing dermal absorption to medium-chain phthalates.

^bGuo and Kannan 2013

Estimates of exposure to DBP from nail polishes were 0.16 and 0.83 µg/kg bw/day for mean and maximum concentrations, respectively.

Other products used by consumers

Globally, DBP may be found in paint products (AGDH 2013a). This use has also been reported in Canada (Environment Canada 2014). In addition, DBP may have applications in the production of articles that may come in contact with skin (ECHA 2012; AGDH 2013a; Environment Canada 2014). DBP was reported in 23 of 35 samples (<3.0-120 mg/kg) of children’s clothing (Brigden et al. 2013). DBP is also found as a non-medicinal ingredient in 1 topical natural health product in Canada (LNHPD modified 2014). The US CPSC CHAP (2014) did not evaluate dermal exposure to items containing DBP.

Exposure to DBP from these uses is considered to be captured by the available Canadian biomonitoring data, therefore estimates of exposure were not calculated.

DEHP

Biomonitoring

Several metabolites of DEHP⁹ were monitored in the CHMS Cycle 1 (2007–2009) and Cycle 2 (2009-2011) with >99% detection in all samples (Health Canada 2011b, 2013). Additionally, these metabolites were measured as part of the First Nations Biomonitoring Initiative (n=492 for on-reserve and Crown-land populations aged 20 years and over). Urine concentrations for MEHP, MEHHP and MEOHP (geometric means) were all reported to be statistically lower in FNBI samples than those reported in CHMS (AFN 2013).

Metabolites of DEHP were also monitored by Health Canada in three cohort surveys: P4 study (n = 31 women and their infants, 542 individual spot samples, women provided multiple urine samples over two visits, monitored 5 metabolites of DEHP¹⁰), MIREC study (n = 1742 pregnant women, spot urine samples, monitored 3 metabolites of DEHP¹¹) and the MIREC-CD Plus study (n = 197 children aged 2 to 3 years, 1 spot

⁹ Mono(2-ethyl hexyl)phthalate [MEHP], Mono(2-ethyl-5-oxohexyl)phthalate [MEOHP], Mono(2-ethyl-5hydroxyhexyl)phthalate [MEHHP]

¹⁰ MEHP, MEOHP, MEHHP, Mono[2-(carboxymethyl)hexyl]phthalate [MCMHP], Mono(2-ethyl-5-hydroxyhexyl)phthalate [MECPP]

¹¹ MEHP, MEOHP, MEHHP

sample per individual, monitored 5 metabolites of DEHP¹²). All three surveys reported high detection frequencies (> 90%) of all metabolites monitored (personal communication from EHSRD, Health Canada, to ESRAB, Health Canada, October 2013, 2014, unreferenced; Arbuckle et al. 2014).

Using the CHMS, P4, MIREC and MIREC-CD Plus datasets, reverse dosimetry intake estimates were generated as previously described. Biomonitoring intakes are presented in Table 9-7 below (see Appendix C for further information on the methodology).

Table 9-7. Biomonitoring daily intakes ($\mu\text{g}/\text{kg bw}/\text{day}$) for DEHP^a

Age group	Study	Male/female	n	Arithmetic mean	50th	75th	95th
1–4 months	P4	males and females	48	0.81	0.42	0.69	1.4
2–3 years	MIREC-CD Plus	males and females	198	3.4	2.6	4.0	8.9
3–5 years	CHMS	males and females	509	5.3	4	6	12 ^b
6–11 years	CHMS	males	256	4.3	3	4.8	12
6–11 years	CHMS	females	250	3.2	2.3	3.2	8.1 ^b
12–19 years	CHMS	males	249	2.1	1.4	2.4	5.6 ^b
12–19 years	CHMS	females	250	2	1.2	1.8	4
18+ years	MIREC	females (pregnant)	1713	3.4	1.6	2.7	8.4
19+ years	P4	females (pregnant)	31 ^c	2.2	1.6	2.3	5.2
20–49 years	CHMS	males	284	1.6	1	1.8	4.9 ^b
20–49 years	CHMS	females	274	1.4	1.0	1.5	2.7
50–79 years	CHMS	males	205	1.3	0.88	1.3	-
50–79 years	CHMS	females	209	1.2	0.94	1.3	2.6

- = No data

^a Data for males and females from: P4 and MIREC pregnant women, P4 infants, MIREC-CD plus children (preliminary results), and CHMS (Cycle 2)

^b Use data with caution

^c n = 31 pregnant women, 542 individual spot samples, women provided multiple urine samples over two visits.

¹² MEHP, MEOHP, MEHHP, MCMHP, MECPP

The highest exposed group based on biomonitoring data (all sources, CHMS) is children aged 3 to 5 years, with median and 95th percentile intakes of 4.0 and 12 µg/kg bw/day, respectively. For older populations (19 years and over), the highest exposed group (all sources, MIREC) is pregnant females aged 18 years and over, with median and 95th percentile intakes of 1.6 and 8.4 µg/kg bw/day, respectively. However, the higher exposure estimates for pregnant women relative to non-pregnant women could be a result of multiple factors (different populations sampled, different sample sizes, etc.) as the results were obtained from different studies. Therefore a correlation between pregnancy and higher DEHP levels cannot be made.

Environmental media and food

The subpopulation with the highest exposure to DEHP from environmental media and food consisted of children (aged 0.5 to 4 years), with total daily intakes of 10.45 and 27.57 µg/kg bw/day estimated on the basis of central tendency and upper-bounding concentrations, respectively (Appendix D, Table D-3a).

Indoor air and dust

One study measured DEHP in indoor air in Canadian homes and reported air concentrations of 88 ng/m³ (median) and a range of 8.8 to 2100 ng/m³ (LOD was not reported; Zhu et al. 2007). Recently, DEHP has also been measured in indoor air in homes in the United States (detected in 100% of 20 samples from homes in Albany, NY, method quantification limit = 0.10 ng/m³, median: 17.4 ng/m³, maximum: 132 ng/m³; Tran and Kannan 2015) and internationally (Blanchard et al. 2014; Lin et al. 2014; Takeuchi et al. 2014). The Canadian indoor air survey concentrations (median: 88 ng/m³ and maximum: 2100 ng/m³; Zhu et al. 2007) were used to estimate the general population daily intake of DEHP from indoor air in Canada (Appendix D, Table D-3a).

DEHP was surveyed in the CHDS and was detected in 100% of homes (range: 35.9 – 3836 µg/g, median: 462 µg/g, 95th percentile: 1880 µg/g) (Kubwabo et al. 2013). Internationally, DEHP has also been reported in house dust (Dodson et al. 2015; Luongo and Östman 2015).

DEHP has applications as a plasticizer in the manufacturing of automobiles and automobile parts (AGDH 2010; ECHA 2012; Environment Canada 2014a). For the general population, indirect exposure (e.g., off-gassing) is considered a relevant source, but no data on this exposure source has been identified, which is currently an uncertainty in the draft screening assessment.

The Canadian survey (Kubwabo et al. 2013) was identified as the key study for exposure characterization, and median (462 µg/g) and 95th percentile (1880 µg/g) concentrations were used to estimate the Canadian general population daily intake of DBP from dust in Canada (Appendix D, Table D-3a).

Food, infant formula and breast milk

In Canada, DEHP presence in food was measured in samples from the 2013 Canadian TDS (Cao et al. 2015). DEHP was detected in 111 of 159 food composite samples (average MDL=39.0 ng/g) with a range of concentrations from 14.4 to 714 ng/g (Cao et al. 2015). Milk, fruits and vegetables are the major sources of intake for all population groups over 1 year of age. Infant formula is the major source of intake for infants under the age of 1 year.

Regarding fruits and vegetables, detectable levels of DEHP (i.e., concentrations above the LOD) were found in most of the composite samples (Cao et al. 2015). The source of DEHP in fruit and vegetable samples is unclear, but could be linked to their packaging. For example, some fruits or vegetables may have been packaged in plastic. Furthermore, certain composite samples included canned or jarred products where coatings and gaskets on jar lids may be potential sources of DEHP in foods. Environmental contamination and agricultural practices are other possible contributors to DEHP residues in fruits and vegetables. Nonetheless, the DEHP results for composite fruit and vegetable samples from the 2013 TDS are considered unusual and unlikely to represent the frequency and magnitude of DEHP concentrations that are typically found in these types of foods (personal communication from Food Directorate, Health Canada, to ESRAB, Health Canada, April 2016; unreferenced). Health Canada's Food Directorate also analyzed composite fruit and vegetable samples from the 2014 TDS in order to further understand the distribution of DEHP concentrations in fruits and vegetables sold in Canada.¹³ Relative to the 2013 TDS data, the 2014 TDS results detected DEHP approximately twofold less frequently in fruit and vegetable composite samples (68% in 2013 versus 30% in 2014). In addition, the mean concentrations in positive samples from 2014 are more than 5 times lower than those from the 2013 TDS samples (61 µg/kg in the 2014 versus 331 µg/kg in 2013). Therefore, the dietary exposures estimates presented herein, which are based only on the 2013 TDS results, are expected to overestimate actual dietary exposure to DEHP (personal communication from Food Directorate, Health Canada, to ESRAB, Health Canada, April 2016; unreferenced).

DEHP presence in food was also monitored as part of the CFIA 2013-2014 and 2014-2015 FSAP surveys (personal communication from Food Directorate, Health Canada, to ESRAB, Health Canada, April 2014; unreferenced). DEHP was detected in 8% of 1518 (LOD: 0.05 µg/g) packaged and processed food samples. DEHP concentrations ranged from 0.27 to 76.2 µg/g, with a mean of the samples of 2.09 µg/g.

Breast milk was monitored as part of the MIREC study. DEHP was detected in 23 samples (n=305, mean of positives=0.0977 µg/g, range= <MDL-0.236 µg/g, average MDL=0.0668 µg/g; personal communication from Food Directorate, Health Canada, to

¹³ The 2014 TDS data were not available at the time that the dietary exposure estimates that are presented in this report were generated.

ESRAB, Health Canada, October 2014; unreferenced). Internationally, DEHP has been detected in breast milk in Sweden (Högberg et al. 2008) and Germany (Fromme et al. 2011), but was not detected in Italy (Guerranti et al. 2013). However, DEHP readily metabolizes to multiple metabolites in the human body (Koch and Calafat 2009) and would therefore not be expected to be found in breast milk in high quantities.

Three metabolites of DEHP¹⁴ were measured in breast milk as part of the P4 study (n = 31 women, 56 breast milk samples collected from study participants). MEHP, MEHHP and MEOHP were detected in 100, 16 and 8% of breast milk samples, respectively (personal communication from EHSRD, Health Canada, to ESRAB, Health Canada, October 2013; unreferenced). LODs were reported to be 0.1, 0.019 and 0.017 µg/L, respectively. The median and maximum reported levels of MEHP were 1.26 and 17.05 µg/L, respectively (personal communication from EHSRD, Health Canada, to ESRAB, Health Canada, October 2013; unreferenced). Internationally, MEHP has also been detected in breast milk in Europe (Mortensen et al. 2005; Högberg et al. 2008; Fromme et al. 2011; Guerranti et al. 2013).

Recently, an analysis of 23 infant formula samples in the P4 study showed 90% detection of MEHP (LOD: 0.1 µg/L) and 8% detection of MEHHP (LOD: 0.019 µg/L). Median and maximum values of MEHP were reported as 0.469 and 2.154 µg/L, respectively. MEOHP was not detected (LOD: 0.017 µg/L) (personal communication from EHSRD, Health Canada, to ESRAB, Health Canada, October 2013; unreferenced). However, measurement of these metabolites in infant formula was affected by high field blank levels (possible contamination) and therefore was not used to quantify intakes. The CFIA surveillance data did detect DEHP in 1 sample of infant cereal (n=7). It was not detected in any samples of infant formula (n=32) or infant foods (n=20) (personal communication from Food Directorate, Health Canada, to ESRAB, Health Canada, April 2014; unreferenced). Internationally, DEHP has been detected in infant formulas in Italy, the UK and Europe (Sørensen 2006; Bradley et al. 2013a; Cirillo et al. 2015).

Using TDS data, probabilistic estimates of dietary intakes for DEHP were derived for the Canadian general population. The results are outlined in Appendix D, Table D-3b and the methodology for estimating probabilistic intakes is provided in Appendix E. Median (1.26 µg/L) and maximum (17.05 µg/L) values of MEHP (metabolite of DEHP) in breast milk measured in the P4 study were used for exposure characterization (Appendix D, Table D-3a). Note that exposure estimates based on food intake are significantly higher than those based on biomonitoring results (see Table 9-7 and Table D-3b). This is expected to be due to detection of frequent and elevated concentrations of DEHP in highly consumed foods from the 2013 TDS, such as certain fruits and vegetables, as previously discussed.

Ambient air, drinking water and soil

¹⁴ MEHP, MEHHP, MEOHP

No Canadian data were identified for DEHP in ambient air. Internationally, DEHP has been reported in outdoor air (Li and Wang 2015). Rudel et al. (2010) measured outdoor air outside homes in the United States (detected in 14% of 43 samples [MRL= 40 ng/m³], median: not reported, maximum: 230 ng/m³). Rudel et al. (2010) was identified as the relevant study for exposure characterization (sampling from North America), and half the MRL (40 ng/m³) and maximum (230 ng/m³) concentrations were used to estimate potential exposures to DEHP via ambient air (Appendix D, Table D-3a).

No Canadian data were identified for DEHP in drinking water. In Canada, Cao et al. (2008) surveyed phthalates in bottled carbonated and non-carbonated water and detected and quantified DEHP in all 11 samples (range: 0.052 to 0.338 µg/L). Internationally, DEHP was also detected and quantified in bottled water (Jeddi et al. 2015), drinking water (Liu et al. 2015), and surface waters (Li et al. 2015; Net et al. 2015; Selvaraj et al. 2015). In the absence of Canadian and North American data on levels of DEHP in tap water, mean (0.102µg/L) and maximum (0.338 µg/L) DEHP concentrations in bottled non-carbonated water were used to estimate the general population daily intake from drinking water (Cao et al. 2008) in Canada (Appendix D, Table D-3a).

Khosravi and Price (2015) reported various phthalates in agricultural soils in both control and biosolid amended soils collected in Nova Scotia, Canada. DEHP was reported at 0.06 ng/g (control soil) and 4.3 ng/g (biosolid amended) (Khosravi and Price 2015). DEHP has also been detected in soils internationally (Cheng et al. 2015; Tran et al. 2015; Wang et al. 2015a). The reported concentration of DEHP in control agricultural soils (0.06 ng/g; Khosravi and Price 2015) was used to estimate potential exposures to DEHP via soil in Canada (Appendix D, Table D-3a).

Products used by consumers

Globally, DEHP may be present in a wide variety of manufactured items, including childcare articles, children's toys, DIY products, electronics, textiles, and gloves (HPD 1993- ; Stringer et al. 2000; AGDH 2010; US CPSC 2010; ECHA 2012; Chao et al. 2013; Korfali et al. 2013). In Canada, DEHP has also been reported as a plasticizer used in various types of manufactured items (NRC 2012; See table 2-2; Environment Canada 2014).

DEHP may be found in paint products (AGDH 2010). The use has also been reported in Canada (Environment Canada 2014).

Globally, DEHP may have applications in the production of articles that may come in contact with skin (HPD 1993- ; AGDH 2010; ECHA 2012; NRC 2012; Chao et al. 2013; US CPSC CHAP 2014). The US CPSC CHAP (2014) reported that dermal exposure to items containing DEHP (i.e., play pen, change pad) would contribute to >10% of exposure to DEHP for infants and children.

Exposure to DEHP from these uses is considered to be captured by the available Canadian biomonitoring data, therefore estimates of exposure were not calculated.

Toys and childcare articles

Numerous studies have examined the concentrations of DEHP in childcare articles and toys (Stringer et al. 2000; Biedermann-Brem et al. 2008; Johnson et al. 2011; Korfali et al. 2013). A summary of DEHP reported in toys and childcare articles available in Canada is presented in Table 9-8.

Table 9-8. Percent content of DEHP in various toys and childcare articles available in Canada

Detection frequency	Percent content	Reference
1 of 117 samples	6.9%	Health Canada 2014 (Canada)
6 of 62 samples	>0.1-37%	Health Canada 2012 (Canada)
15 of 38 samples	>0.1-54%	Health Canada 2009 (Canada)
33 of 72 samples	>0.1-22.8%	Health Canada 2007 (Canada)

Currently, Canada (like the United States and the European Union) has regulations in place limiting the amount of certain phthalates (including DEHP) in toys and childcare articles (*Phthalates Regulations* under the *Canada Consumer Product Safety Act* [Canada 2016]). The EU's RAPEX database also shows low reporting of toys tested in violation of the regulation for DEHP (RAPEX 2015), and the US CPSC recently stated that less than 10% of exposures to DEHP for infants and children would result from mouthing of toys and childcare articles (US CPSC CHAP 2014).

Given the absence of DEHP in toys and childcare articles reported in Canadian monitoring studies and the low frequency and low percent content of DEHP reported in international monitoring studies, exposure was not quantified and oral intakes from mouthing of toys and/or childcare articles were not estimated.

Cosmetics

On the basis of notifications submitted under the *Cosmetic Regulations*, DEHP is not expected to be present in cosmetics in Canada (personal communication from the CPSC, Health Canada, to ESRAB, Health Canada, July 2015; unreferenced). However, DEHP has been detected in various types of cosmetics and personal care products in Canada (Koniecki et al. 2011) and internationally (Guo and Kannan 2013; Guo et al. 2013). Liang et al. (2013) did not detect DEHP in cosmetics in China. DEHP has also been reported in some fragrance products (0-46ppm; Not too Pretty 2015). This presence may be due to potential migration from packaging. A summary of recent

studies measuring concentrations of DEHP in cosmetics and personal care products reported in North America is outlined in Table 9-9.

Table 9-9. Concentrations of DEHP in cosmetics and personal care products

Detection frequency and product types ^a	Concentration (µg/g)	Reference (country)
5% of 85 fragrance, haircare and deodorant products	ND-521	Koniecki et al. 2011 (Canada)
4% of 69 nail polish, lotion and skin cleanser products	ND-1045	Koniecki et al. 2011 (Canada)
1% of 98 baby products	ND-15	Koniecki et al. 2011 (Canada)
76% of 41 rinse-off products	ND-6.15	Guo and Kannan 2013 (United States)
66% of 109 leave-on products	ND-135	Guo and Kannan 2013 (United States)
40% of 20 baby products	ND-8.22	Guo and Kannan 2013 (United States)

^a Limits of detection: Koniecki et al. 2011 (0.1 µg/g), Guo and Kannan 2013 (0.01 µg/g)

DEHP is on the *List of Prohibited and Restricted Cosmetic Ingredients in Canada* (Health Canada 2011a) and was not reported as used in Canada (July 2015 email from the CPSD to ESRAB, Health Canada). Additionally, the Canadian study reported that detection frequencies are low (1% to 5%) and a majority of the concentrations in all studies are in the sub-ppm range. Consequently, exposure to DEHP from personal care products and cosmetics is not considered to be significant. Exposure estimates from this source were not generated.

Adult toys

No Canadian use of DEHP in adult toys was reported under the CEPA section 71 industry survey (Environment Canada 2014). Global use patterns suggest that there is potential for use of DEHP in adult toys. DEHP was reported in 8 of 15 adult toys sampled in the EU, with concentrations ranging from 0.73 to 702 mg/g (Bavarian State Ministry of the Environment and Public Health 2012). The Danish Environmental Protection Agency published a report assessing exposure to DEHP from these products and derived intakes of 1.7 and 47 µg/kg bw/day, for normal-case and worst-case exposures, respectively (Nilsson et al. 2006).

Medical devices

Globally, DEHP is reported to be used in medical applications (ECHA 2012). Medical devices may therefore be a potential source of DEHP exposure. Currently, Canada has guidance in place for DEHP in medical devices. However, given the lack of data and uncertainty in quantifying estimates of exposure from medical devices, this exposure

source was not quantified and is currently an uncertainty in this draft screening assessment.

DnHP

No data was identified for DnHP in air or water; therefore, intakes from these sources were not estimated.

DnHP was surveyed in the CHDS and was detected in 98% of homes (range: ND–264 µg/g, median: 3.8 µg/g, 95th percentile: 62 µg/g) (Kubwabo et al. 2013). DnHP has also been reported in house dust in the United States (Dodson et al. 2015). The Canadian survey (Kubwabo et al. 2013) was identified as the key study for exposure characterization, and median (3.8 µg/g) and 95th percentile (62 µg/g) concentrations were used to estimate the Canadian general population daily intake of DnHP from dust (Appendix D, Table D-4a).

No Canadian or North American data were identified for DnHP in soil. DnHP has been detected in 100% of urban (n=17; median=0.018 µg/g, maximum=0.019 µg/g), suburban (n=28; median=0.016 µg/g, maximum=1.227 µg/g) and rural (n=37; median=0.016 µg/g, maximum=0.1 µg/g) soils in China (Hongjun et al. 2014). Given the limited data available on DnHP in soil, exposure intakes from this source were not estimated.

No Canadian data for DnHP in foods were found. One US study looked at many phthalates, including DnHP, in a variety of food items (Schechter et al. 2013). Data from this US study were employed to generate dietary exposure estimates using a probabilistic approach (Appendix D, Table D-4b).

The subpopulation with the highest exposure from dust and food consisted of infants (0 to 6 months old), with total daily intakes of 0.019 and 0.31 µg/kg bw/day estimated on the basis of central tendency and upper-bounding concentrations, respectively (Appendix D, Table D-4a).

Given the absence of reporting to the CEPA section 71 industry survey (Environment Canada 2014), and the lack of information as to DnHP presence in product databases, general population exposure to DnHP from products used by consumers is expected to be negligible.

DIOP

No data was identified for DIOP in air, water, soil or food; therefore, intakes from these sources were not estimated.

DIOP was surveyed in the CHDS and was detected in 87% of homes (range: ND–1165 µg/g, median: 6.6 µg/g, 95th percentile: 28.6 µg/g) (personal communication from EHSRD, Health Canada, to ESRAB, Health Canada, August 2014; unreferenced). These data were identified as the key study for exposure characterization, and median

(6.6 µg/g) and 95th percentile (28.6 µg/g) concentrations were used to estimate the Canadian general population daily intake of DIOP from dust (Appendix D, Table D-5).

In Canada, DIOP has also been reported as a plasticizer used in various types of manufactured items (See Table 5-1; Environment Canada 2014). However, given the low volume of DIOP reported in Canada (See table 4-2), exposure estimates from products used by consumers were not estimated.

The subpopulation with the highest exposure from dust consisted of infants (0 to 6 months old), with total daily intakes of 0.033 and 0.14 µg/kg bw/day estimated on the basis of central tendency and upper-bounding concentrations, respectively (Appendix D, Table D-5).

9.1.3 Long-chain phthalates

For detailed information on long-chain phthalates included in this section, please refer to the SOS report on long-chain phthalates esters (Environment Canada, Health Canada 2015d).

DIDP

Exposure estimates were calculated using biomonitoring results as well as data on DIDP occurrence in dust, food and plastic items. They are presented in the LCP SOS report (Environment Canada, Health Canada 2015d) and summarized below. Recently, DIDP has been reported internationally in soils (Tran et al. 2015), indoor air (Takeuchi et al. 2014), settled dust (Luongo and Östman 2015), and tap water (Yang et al. 2014). However, these reported values did not change the exposure estimates presented previously (Environment Canada, Health Canada 2015d).

The highest exposed group according to biomonitoring data (all sources, NHANES) is male children aged 6 to 11 years, with median and 95th percentile intakes of 1.4 and 4.4 µg/kg bw/day respectively. For older populations, the highest exposed group (all sources, NHANES) is adults over 20 years of age, with median and 95th percentile intakes of 0.76 and 4.4 µg/kg bw/day, respectively, for males, and 0.65 and 4.9 µg/kg bw/day, respectively, for females.

The subpopulation with the highest exposure from dust and food consisted of infants (6 months to 4 years old), with total daily intakes of 0.514 and 2.87 µg/kg bw/day estimated on the basis of central tendency and upper-bounding concentrations, respectively. For populations aged 12 years and over, the highest exposed group is adolescents (aged 12 to 19 years), with total daily intakes of 0.075 and 0.726 µg/kg bw/day estimated on the basis of central tendency and upper-bounding concentrations, respectively.

Estimated daily intakes for infants from dermal exposure to DIDP from plastic items, based on lower-end and upper-bounding exposure scenarios, were 0.27 and 2.16 µg/kg

bw/day, respectively. For adults exposed to plastic items (females aged 20 years and over), estimated daily intakes, based on lower-end and upper-bounding exposure scenarios, were 0.27 and 0.85 µg/kg bw/day, respectively.

DUP

Exposure estimates were calculated using data on DUP occurrence in dust and plastic items. Since the publication of the LCP SOS report, DUP has been analyzed in foods included in the 2013 Canadian Total Diet Study and was not quantified above the method detection limit (average MDL= 6.97 ng/g; Cao et al. 2015). Exposure estimates for DUP are presented in the LCP SOS report (Environment Canada, Health Canada 2015d) and summarized below.

The subpopulation with the highest exposure from dust consisted of infants (0 to 6 months old), with total daily intakes of 0.0198 and 0.349 µg/kg bw/day estimated on the basis of central tendency and upper-bounding concentrations, respectively. For populations aged 12 years and over, the highest exposed group is adolescents (aged 12 to 19 years), with total daily intakes of <0.001 and 0.004 µg/kg bw/day estimated on the basis of central tendency and upper-bounding concentrations, respectively.

Estimated daily intakes for infants from dermal exposure to DUP from plastic items, derived on the basis of lower-end and upper-bounding exposure scenarios, were 2.7 and 21.6 µg/kg bw/day, respectively. For adults exposed to plastic items (females aged 20 years and over), estimated daily intakes, based on lower-end and upper-bounding exposure scenarios, were 2.7 and 8.5 µg/kg/day, respectively.

9.2 Health effects assessment

As described in detail in the SOS reports (Environment Canada, Health Canada 2015a,b,c,d), critical effects of phthalates (i.e., medium-chain phthalates) consist of adverse effects on the development of the male reproductive system following exposure. The spectrum of effects on male reproductive development has been described as the “rat phthalate syndrome” (RPS) and although primarily studied in rats, it has also been demonstrated in other species. The effects include alterations of feminization parameters (decreased anogenital distance [AGD] in pups and nipple retention [NR] in juveniles), reproductive tract malformations (cryptorchidism [CRY], hypospadias [HYP], testicular pathological changes [TP]) and effects on fertility (sperm counts, motility and quality at adulthood). Similar to the SOS reports, the hazard assessment is structured to present information at three different life stages (gestational exposure [GD0-21], (pre)pubertal-pubertal [PND1-55] and adult [PND55+], with particular focus on the male gender because of the varying degrees of sensitivity at different life stages. When there was limited information or absence of data for a particular phthalate at a specific life stage or exposure period (as it is the case for DMP, DIBP, DMCHP, DBzP, B84P, B79P, CHIBP, BChP, BIOP, and DUP), read-across was applied based on health effects of the closest analogue(s) (Health Canada 2015). In addition, potential effects of phthalates on humans were evaluated following the same

approach as previously described in the SOS reports (Environment Canada, Health Canada 2015a,b,c,d).

9.2.1 Short-chain phthalates

DMP

The SCP SOS (Environment Canada, Health Canada 2015a) summarizes the health effects literature related to DMP and its analogue DEP. No new animal hazard data were identified after the literature cut-off date of the SCP SOS.

Tables 9-10, 9-11 and 9-12 provide critical endpoints and corresponding no-observed-effects level (NOEL) and/or lowest-observed effects level (LOEL) values for DMP, as previously described in SCP SOS (Environment Canada, Health Canada 2015a) that will be used for risk characterization.

Table 9-10. Summary results of reproductive and/or developmental effects studies based on oral exposure to DMP

Life stage	Species	Effect (mg/kg-bw/day)	LOEL (mg/kg-bw/day)	NOEL (mg/kg-bw/day)	Reference
In utero	Rat	No developmental effects observed. No effects on RPS parameters (GD14-PND3)	NA	750	Gray et al. (2000); Furr et al. (2014)
(Pre)pubertal	Rat (7 d)	A significant decrease in serum and testicular testosterone* , dihydrotestosterone concentrations and ↑ absolute, relative liver weight	1862 (LOAEL)	N/A	Oishi and Hiraga (1980a)
Adult	Rat DEP (F0, 8 wk)	↓ serum testosterone, transient increases in abnormal and tailless sperm at the mid dose, (not high), ↓ in absolute epididymis, adrenal weights	1016	197	Fujii et al. (2005)

*These results are of uncertain adversity since no other effects in testes were noted (no changes in testes weights, no inhibition of spermatogenesis, and no testicular atrophy).

N/A = Not applicable

Table 9-11. Summary results of reproductive and/or developmental effects studies based on dermal exposure to DMP

Life stage	Species	Effect (mg/kg-bw/day)	LOEL (mg/kg-bw/day)	NOEL (mg/kg-bw/day)	Reference
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In utero	Rat (GD1-20)	LOEL (Maternal) = 2380 (slight ↓body weight). No effects on pups	N/A	2380	Hansen and Meyer (1989)
(Pre)pu bertal	Rat DEP (4 wk)	Systemic LOEL = 1332 ↑relative kidney and liver (2278) weights, no testicular pathology observed	N/A	2278	NTP (1995)
Adult	Rat DEP (2 yr)	Systemic LOAEL = 743 ↓absolute brain weight, no testicular pathology observed	N/A	743	NTP (1995)

N/A = Not applicable

Table 9-12. Summary table of critical systemic effects after dermal exposure to DMP

Endpoint	Species	Effect	LOAEL (mg/kg-bw/day)	NOAEL (mg/kg-bw/day)	Reference
Subchronic	Rat (90 days)	Changes in nervous system and renal function in males	1250	200	Timofieyskaya (1976)
Chronic	Rats DEP (2 years)	Small but significant decrease in absolute brain weight in males	743	230	NTP (1995)
Chronic	Mice DEP (2 years)	Decrease in mean body weight in females	834	415	NTP (1995)

Evidence in humans

A literature update was also conducted to identify any recent human data for short-chain phthalates. The updated search was focused on reproductive and developmental endpoints in males because these endpoints were identified as critical health endpoints in the SOS reports. Studies were further evaluated and scored for quality using a consistent evaluation metric (Downs and Black 1998). For the health outcomes evaluated (i.e., sex hormone levels, anogenital distance, birth measures, male infant genitalia, preterm birth and gestational age, altered male puberty, gynecomastia, changes in semen parameters, pregnancy loss, and altered time to pregnancy), there was inadequate evidence or no evidence of associations between DMP and the reported outcomes (Table 9-13). More detail is provided in Health Canada (2016a) available upon request.

Table 9-13. Summary of levels of evidence of associations between short-chain phthalates and health outcomes

Outcome	DMP (MMP)
Sex hormone levels	IA (7)
Anogenital distance	NA (1)
Birth measures	NA (4)
Male infant genitalia	NA (1)
Preterm birth and gestational age	NA (2)
Altered male puberty	IA (3)
Gynecomastia	NM
Changes in semen parameters	IA (5)
Pregnancy loss	NA (2)
Altered time to pregnancy	IA (1)

() = Number of studies

NM = Not measured in studies of quartile 2 and above (See Health Canada [2016a] for more details).

NA = No evidence of association.

IA = Inadequate evidence of an association.

LA = Limited evidence of an association.

MMP = Monomethyl phthalate.

9.2.2 Medium-chain phthalates and additional phthalates

9.2.2.1 Medium-chain phthalates

DIBP

The MCP SOS (Environment Canada, Health Canada 2015b) summarizes the health effects literature related to DIBP. No new animal hazard studies were identified for this phthalate after the literature cut-off date of the MCP SOS.

Table 9-14 provides critical endpoints and corresponding no-observed-adverse-effects level (NOAEL) and/or lowest-observed-adverse-effects level (LOAEL) values for DIBP, as previously described in MCP SOS (Environment Canada, Health Canada 2015b), that will be used for risk characterization. DIBP has low systemic toxicity as described in MCP SOS (Environment Canada, Health Canada 2015b); hence, no systemic critical effects were established.

Table 9-14. Summary of critical effect levels for reproductive and/or developmental effects after oral exposure to DIBP

Life stage during which exposure occurred	Species	Effects	LOAEL (mg/kg-bw/day)	NOAEL (mg/kg-bw/day)	Reference
In utero (GD12–21)	Rat	↓AGD, ↓NR, effects on fertility and other RPS effects; decreased testicular testosterone	250	125	Saillenfait et al. 2008; Furr et al. 2014

		production			
(Pre) pubertal	Rat	↑apoptotic spermatogenic cells, ↓ testes weight and vimentin filament disorganization in Sertoli cells	500	300	Zhu et al. 2010
Adult	Rat (DBP)	Testicular pathology, effects on sperm count and motility, and decreased ROW	500	250	Srivastava et al. 1990a; Zhou et al. 2011c

DCHP

The MCP SOS (Environment Canada, Health Canada 2015b) summarizes the health effects literature related to DCHP. A literature update identified new developmental and genotoxicity studies, which are summarized in Tables 9-15 and 9-16. In Li et al. (2016), rats were exposed to 0, 10, 100 or 500 mg/kg-bw/day DCHP from GD12-21. The body weight of male pups was significantly reduced in treated animals. DCHP dose-dependently increased abnormal fetal cell aggregation and decreased fetal Leydig cell size, cytoplasmic size and nuclear size at all doses tested. Decreases in AGD and increased incidences of MNGs were noted at 100 mg/kg-bw/day and above. In another study, the authors also examined the effects of in utero DCHP exposure on offspring development (Ahabab and Barlas 2015). Rats were exposed to 0, 20, 100 or 500 mg/kg-bw/day DCHP from GD6-19. Maternal effects were not observed. An increase in resorption was observed in all treated groups. A decrease in AGD and testicular pathological changes were observed starting from 20 mg/kg-bw/day. The LOAELs of these studies are lower than the lowest NOAEL previously identified in the MCP SOS for DCHP (Environment Canada, Health Canada 2015b). As described in the MCP SOS for DCHP, a decrease in AGD was observed at higher doses in both F1 (at 511 mg/kg-bw/day) and F2 (from 107 mg/kg-bw/day) generations in a two-generation study with a NOAEL of 21 mg/kg-bw/day (Hoshino et al. 2005), suggesting transgenerational effects induced by DCHP. The dose level of 16 to 21 mg/kg-bw/day from this two-generation study was also identified as the NOAEL for developmental effects by the Australian National Industrial Chemicals Notification and Assessment Scheme (NICNAS) (AGDH 2008) and the US CPSC CHAP (2014). Different strains of rats were used by Ahabab and Barlas (2015) than by Hoshino et al. (2005) and Li et al. (2016) (Wistar vs Sprague Dawley, respectively). The lowest LOAELs identified for developmental toxicity were 10 to 20 mg/kg-bw/day estimated on the basis of testicular pathological changes from 10 mg/kg-bw/day, reduced AGD, and increased resorption from 20 mg/kg-bw/day (Ahabab and Barlas 2015; Li et al. 2016).

Table 9-15. Summary of new DCHP developmental studies identified since the publication of the MCP SOS report. Effects from gestational exposure to DCHP in male offspring (mg/kg-bw/day)

Strain and species; dose (mg/kg-bw/day); route; duration (reference) CAS RN	Testosterone levels ^a (T, S)	Feminization parameters ^b	Reproductive tract malformations and/or fertility ^c	Other developmental parameters ^d	Maternal effects
DCHP Sprague Dawley rats; 0, 10, 100, 500; gavage; GD12-21 (Li et al. 2016)	100 (T) NM (S)	100 (AGD) NM (NR) NM (PPS)	NM (CRY) NM (HYP) 10 ^e (TP- ↑ abnormal fetal leydig cell aggregation, ↓ fetal Leydig cell size, cytoplasmic size and nuclear size, ↑ MNGs at 100) NM (FER)	10 ^e (↓ BW) NM (ROW) NE (FV) NM (EMB) NM (ESV)	NE
DCHP Wistar albino rats; 0, 20, 100, 500; gavage; GD6-19 (Ahabab and Barlas 2015)	NM (T) 100 (S)	20 ^{e, f} (AGD) NM (NR) NM (PPS)	NM (CRY) NM (HYP) 20 ^e (TP- ↑ atrophic and small seminiferous tubules, ↓ no. of germ cells in tubules, cells detach from tubule wall, ↑ Leydig cell clusters) NM (FER)	20 ^e (↑ BW @ 20, 100) NM (ROW) NE (FV) 20 ^{e, f} (EMB-resorption) NM (ESV)	NE

^aTestosterone levels measured (can include quantity/production) at varying days post-birth. T=Testicular testosterone; S=Serum testosterone.

^bFeminization parameters can include anogenital distance (AGD), nipple retention (NR), preputial separation (PPS).

^cMalformations include: cryptorchidism (CRY), hypospadias (HYP), testicular pathology (TP), including multinucleated gonocytes (MNG), and/or reproductive effects such as fertility (FER) in offspring (sperm number, motility) or reproductive success at adult stage after in utero exposure.

^dOther developmental effects include: decreases in overall fetal body weight (BW), decreases in reproductive organ weight (ROW), fetal viability (FV), embryotoxicity (EMB), or on the incidence of external, skeletal or visceral malformations (ESV).

^e Lowest dose measured in the study.

^f Absolute AGD, AGD relative to BW and AGD relative to cube root of BW at birth were reported in the study and reached statistically significant different from control animals at 20 mg/kg-bw/day (Ahabab and Barlas 2015). NM = not measured.

NE = no effect observed at the dose range tested. When NE is presented alone in the first four columns of effects, all parameters in the footnote description were measured and no statistically significant effects were observed in the endpoints at the dose range administered.

Table 9-16 Summary of new literature of DCHP identified since the publication of the MCP SOS report

Endpoint	Study details	Results	Reference
Genotoxicity (<i>in vivo</i>)	TUNEL assay Species/strain: female Wistar albino rat Route: oral (gavage) Dose and duration: 0, 20, 100 or 500 mg/kg-bw/day during GD6-19 (10/dose) Testicular samples were collected from different life stages (prepubertal PD20, pubertal PD21, adult PD90) of the pups (n=8–10/group).	Dose-response increase in apoptotic cells was observed in prepubertal and pubertal life stages, but not in the adult life stage	Ahbab et al. 2014
Genotoxicity (<i>in vivo</i>)	Comet assay Species/strain: female Wistar albino rat Route: oral (gavage) Dose and duration: 0, 20, 100 or 500 mg/kg-bw/day during GD6-19 (10/dose) Testicular and blood samples were collected at the adult life stage (PD90) of the pups (n=7–10/group)	Increase in DNA breakage was only observed in the low doses with no clear dose-response pattern	Ahbab et al. 2014

As described in the MCP SOS for DCHP (Environment Canada, Health Canada 2015b), only one limited repeat-dose oral exposure study with DCHP was identified in sexually immature animals. That study was determined to be limited and was not used to characterize risk of DCHP for this life stage. Therefore, results from the two-generation study (Hoshino et al. 2005) described in the MCP SOS were used, particularly observations reported in the F1 males exposed in utero to DCHP through lactation and via diet from PND21 for at least 10 weeks until necropsy. The NOAEL for the reproductive toxicity of DCHP at the prepubertal-pubertal life stage was 18 mg/kg-bw/day in F1 males, based on observed decreases in spermatid head counts and testicular atrophy starting from 90 mg/kg-bw/day. Reduced body weight gain and reduced food consumption were observed in F1 males at 90 mg/kg-bw/day and above. It is recognized that this effect level is conservative as animals had been exposed during early development before the prepubertal-pubertal life stage.

Tables 9-17 and 9-18 provide the critical endpoints and corresponding NOAEL and/or LOAEL values for DCHP that will be used for risk characterization.

Table 9-17. Summary of critical effect levels for reproductive and/or developmental effects after oral exposure to DCHP

Life stage	Species	Effects	LOAEL (mg/kg-bw/day)	NOAEL (mg/kg-bw/day)	Reference
In utero	Rat	Testicular pathological changes, decreased AGD and increased resorption	10–20	N/A	Ahbab and Barlas 2015; Li et al. 2016
(Pre)pubertal	Rat	Decrease in spermatid head counts, testicular atrophy, reduced body weight gain and reduced food consumption in F1 males	90	18	Hoshino et al. 2005
Adult	Rat	Slight focal seminiferous tubule atrophy in 1 male at highest dose, with decreased body weight gain	402 (6000 ppm LOEL)	80 (1200 ppm)	Hoshino et al. 2005

N/A = Not applicable

Table 9-18. Summary table of critical systemic effects after oral exposure to DCHP

Endpoint	Species	Effect	LOAEL (mg/kg-bw/day)	NOAEL (mg/kg-bw/day)	Reference
Subchronic	Rat (90 days)	Increase in liver weight (females)	75	25	de Ryke and Willems 1977

DMCHP

As described in the MCP SOS (Environment Canada, Health Canada 2015b), DCHP was used as an analogue as no studies examining the potential health effects of DMCHP were identified for any species or gender. No new literature on DMCHP was identified after the literature cut-off date of the MCP SOS. See the above section for a summary of the critical health effects used for this phthalate.

DBzP

The MCP SOS (Environment Canada, Health Canada 2015b) summarizes the health effects literature related to DBzP and its analogue MBzP. No new literature was identified after the literature cut-off date of the MCP SOS. Table 9-19 provides the critical endpoints and corresponding NOAEL and/or LOAEL values for DBzP, as previously described in MCP SOS (Environment Canada, Health Canada 2015b), that will be used for risk characterization.

Table 9-19. Summary of critical effect levels after oral exposure to DBzP using MBzP as closest analogue

Life stage	Species	Effects	LOAEL (mg/kg-bw/day)	NOAEL (mg/kg-bw/day)	Reference
In utero	Rat (MBzP)	↓ AGD and ↑ cryptorchidism	250	167* (systemic toxicity LOAEL based on ↓ food consumption, ↓ BW)	Ema et al. 2003
(Pre)pubertal/adult	Rat (MBzP)	↓ sperm count (20%)	250 (LOEL)	N/A	Kwack et al. 2009

* Maternal toxicity at this dose, but considered not a factor in selection of adverse effects in male offspring.
N/A = Not applicable.

B84P

The MCP SOS (Environment Canada, Health Canada 2015b) summarizes the health effects literature related to B84P and its analogues. No new literature was identified for B84P after the literature cut-off date of the MCP SOS. Tables 9-20 and 9-21 provide the critical endpoints and corresponding NOAEL and/or LOAEL values for B84P, as previously described in MCP SOS (Environment Canada, Health Canada 2015b) that will be used for risk characterization.

Table 9-20. Summary of critical effect levels for reproductive and/or developmental effects after oral exposure to B84P

Life stage	Species	Effects	LOAEL (mg/kg-bw/day)	NOAEL (mg/kg-bw/day)	Reference
In utero	Rat (BBP)	Decreased body weight (F1/F2 males and females) and ↓ AGD at birth in F2 males ^a ; ↓ testicular testosterone	100	50	Aso et al. 2005; Nagao et al. 2000; Tyl et al. 2004; Furr et al. 2014
(Pre)pubertal	Rat (MBzP)	↓ sperm counts and sperm motility	250 (LOEL)	N/A	Kwack et al. 2009
(Pre)pubertal	Rat (BBP)	↓ sperm counts and sperm motility	500 (LOEL)	N/A	Kwack et al. 2009
Adult	Rat (BBP)	reduced absolute epididymal weight,	400	200	Aso et al. 2005

		hyperplasia of the Leydig cells in the testes and decreased spermatozoa in the lumina of the epididymis			
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^a A statistically significant increase of AGD in F1 and decreased pup weight on PND0 in F2 female offspring at 100 mg/kg-bw/day and above was also reported.
N/A = Not applicable.

Table 9-21. Summary table of critical systemic effects after oral exposure to B84P

Endpoint	Species	Effect	LOAEL (mg/kg-bw/day)	NOAEL (mg/kg-bw/day)	Reference
Subchronic	Rat (3 months) (BBP)	Histopathological changes in the pancreas, gross pathological alterations in the liver and a significant increase in relative kidney weight in male rats	381	151	Hammond et al. 1987

DIHepP

The MCP SOS (Environment Canada, Health Canada 2015b) summarizes the health effects literature related to DIHepP. No new literature was identified after the literature cut-off date of the MCP SOS. Tables 9-22 and 9-23 provide the critical endpoints and corresponding NO(A)EL and/or LO(A)EL values for DIHepP, as previously described in MCP SOS (Environment Canada, Health Canada 2015b), that will be used for risk characterization.

Table 9-22. Summary of critical effect levels for reproductive and/or developmental effects after oral exposure to DIHepP

Life stage	Species	Effects	LOAEL (mg/kg-bw/day)	NOAEL (mg/kg-bw/day)	Reference
In utero	Rat	Significant reduction in AGD in male F2 pups	309–750	64–168	McKee et al. 2006
(Pre) pubertal	Rat	Significant reduction in AGD; delayed preputial separation, nipple retention, hypospadias	419–764	227–416	McKee et al. 2006

		and cryptorchidism in F1 pups			
Adult	Rat	No adverse effects up to the highest dose level tested	N/A	404–623	McKee et al. 2006

N/A = Not applicable

Table 9-23. Summary table of critical systemic effects after oral exposure to DIHepP

Endpoint	Species	Effect	LOAEL (mg/kg-bw/day)	NOAEL (mg/kg-bw/day)	Reference
Subchronic	Rat	Increased liver and kidney weights with histopathological findings in F0	222–716	50-162	McKee et al. 2006
Chronic	Rat	Increased liver and kidney weights associated with centriobular hypertrophy in males and females in F1	227–750	50-168	McKee et al. 2006

B79P

The MCP SOS (Environment Canada, Health Canada 2015b) summarizes the health effects literature related to B79P and its analogues. New key studies were identified after the literature cut-off date of the MCP SOS, which are described in the following sections and will be used for risk characterization.

Early development: in utero exposure to B79P

Three oral rat studies were found focusing on effects of B79P during development, including one study that was previously described in the MCP SOS. These studies all examined the effects of B79P when administered during gestation in pregnant rats during the fetal masculinization programming window GD15-17. Summaries of the studies are described in Table 9-24 below.

In an industry submitted developmental study, Tyl et al. (2012) exposed Sprague-Dawley rats to B79P via the diet from GD6-20, at target concentrations of 0, 250, 750 or 3750 ppm (reported intakes: 0, 19, 58 and 288 mg/kg-bw/day). There were no effects on maternal body weight, although food consumption was significantly increased in a dose-related manner in the two highest dose groups for the exposure. At necropsy, both absolute and relative liver weights were significantly increased at the highest dose; no adverse effects were observed at histological examination. There was no effect on the

mean number of live fetuses per litter or fetal body weight. There were no differences among groups in the incidence (fetal or litter) of either external malformations/variations or of skeletal malformations. Similarly, there were no differences in the total number of malformations (external, visceral, skeletal). The authors concluded that there had been maternal toxicity at the highest dose only, with increased absolute and relative liver weights and “no adverse findings in the prenatal offspring at any dose.” Parameters specific to RPS (AGD, NR, PPS, etc) were not reported.

In a second industry submitted study, Tyl et al. (2013) also conducted a two-generation reproductive toxicity study with Sprague-Dawley rats exposed to B79P at 0, 250, 750, 2500 and 5000 ppm (estimated doses: 0, 19, 56, 188 and 375 for males and 0, 17, 50, 167 and 333 mg/kg-bw/day for females). F0 and F1 male and female rats were exposed for 10 weeks pre-mating and 2 weeks mating. Female rats were also exposed throughout gestation (approximately 3 weeks) and lactation (3 weeks). There were no differences in maternal or offspring lactational parameters or in F1 litter parameters on PND 0-4. No effects were observed in AGD across groups. No differences were observed in acquisition of PPS in F1 males. There was no evidence of effects on mating, production of litters, or litter size. Other parameters specific to RPS, specifically NR, HYP and CRY, were not reported.

In the F2 generation, there were no differences in total litter size, live litter size, live birth ratio, survival ratio, AGD, pup body weight or gross pathology. Relative liver weight was increased in both F2 males. The authors concluded that B79P was “clearly not a reproductive toxicant in either sex” at exposures up to 333–375 mg/kg-bw/day. However, a NOAEL of 50–56 mg/kg-bw/day was assigned for systemic toxicity on the basis of reduced body weights and altered organ weights and organ/body weight ratios, affecting the liver and kidney, which were free from gross and histopathologic changes (Tyl et al. 2013).

Table 9-24. Effects from gestational exposure to B79P in male offspring (mg/kg-bw/day)

Strain and species; dose (mg/kg-bw/day); route; duration (reference) CAS RN	Testosterone levels ^a (T, S)	Feminization parameters ^b	Reproductive tract malformations and/or fertility ^c	Other developmental parameters ^d	Maternal effects
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<p>B79P SD Rats: 0, 750, 3750, 7500 ppm; est. 0, 50, 250, 500 (diet) GD6 – PND 21 Cited in REACH Dossier; ECHA 2013a</p>	<p>NM</p>	<p>50^e (at PND1 both sexes) (AGD) 250 (at PND21 for males) 500^f (NR) NR (PPS)</p>	<p>50^{e, f} (CRY) 250^f (HYP, epispadias) 500 (TP) NM (FER)</p>	<p>50^e (BW @ lactation) NM (ROW) NE (FV) NE (EMB) NR (ESV)</p>	<p>250 (↑ liver and kidney weights, ↓ body wt)</p>
<p>SD Rats: 0, 250, 750, 2500, 5000 ppm; F0 Female intake during gestation est. 0, 17, 50, 167, 333 (diet) 2-gen Tyl et al. (2013)</p>	<p>NM</p>	<p>NE (AGD @PND0) NE^g (NR) NE (PPS)</p>	<p>NM (CRY) NM (HYP) NE (TP-adult) NE (FER)</p>	<p>167 (BW 11.6%@PND7-14) NE (ROW) NE (FV) NE (EMB) NE (ESV) 177 (OW -↑ rel liver wt) 336 (↓abs brain, spleen, thymus weight)</p>	<p>17 (↓ body wt gain at this dose only during gestation) 167 (↑relative liver and kidney weights, no histopathological findings) 333 (small ↑ bilateral cortical vacuolation of adrenal glands)</p>
<p>SD Rats: 0, 250, 750, 2500, 5000 ppm; F1 Female intake during gestation est. 0, 17, 50, 167, 333 (diet) 2-gen Tyl et al. (2013)</p>	<p>NM</p>	<p>NE (AGD) NM (NR) NM (PPS)</p>	<p>NM (CRY) NM (HYP) NE (TP) NE (FER)</p>	<p>NE (BW) NE (ROW) NE (FV) NE (EMB) NE (ESV) 333 (OW - ↑ relative liver weight)</p>	<p>NE (BW) 167 (↑relative and absolute liver weights, no histopathological findings) 333 (small ↑ bilateral cortical vacuolation of adrenal glands in 2 females)</p>
<p>B79P SD Rats: 0, 250, 750, 3750 ppm; est. 0, 16.7, 50, 250 (diet) GD6–</p>	<p>NM</p>	<p>NM (AGD) NM (NR) NM (PPS)</p>	<p>NM (CRY) NM (HYP) NM (TP) NM (FER)</p>	<p>NE (BW) NM (ROW) NE (FV) NE (EMB) NE (ESV)</p>	<p>50 (↑ food cons) 250 (↑ absolute and relative liver weights (7.6%, no histopathological findings)</p>

20 Tyl et al. (2012)					
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^aTestosterone levels measured (can include quantity/production) at varying days post-birth. T=Testicular testosterone; S=Serum testosterone.

^bFeminization parameters can include anogenital distance (AGD), nipple retention (NR), preputial separation (PPS).

^cMalformations include: cryptorchidism (CRY), hypospadias (HYP), testicular pathology (TP), and/or reproductive effects such as fertility (FER) in offspring (sperm number, motility) or reproductive success at adult stage after in utero exposure.

^dOther developmental effects include: decreases in overall fetal body weight at PND 1 (BW), decreases in reproductive organ weight (ROW), fetal viability (FV), embryotoxicity (EMB), or on the incidence of external, skeletal or visceral malformations (ESV). Other organ weights (OW).

^eLowest dose tested in the study.

^fCYP, HYP and NR effects were observed on PND21, but not on PND75 where these animals were exposed until PND21 (ECHA 2013b).

^gNR result was based the executive summary of the study saying there were no effects in both F1 and F2. No additional info on NR was found in the rest of the report (Tyl et al. 2013).

NM = Not measured.

NE = No effect observed at the dose range tested. When NE is presented alone in the first 4 columns of effects, all parameters in the footnote description were measured and no statistically significant effects were observed in the endpoints at the dose range administered.

Overall, the highest NOAEL identified for developmental toxicity of B79P after gestational exposure was 50 mg/kg-bw/day based on decreased AGD in male pups and increased incidence of epispadias on PND21 observed at the next dose level of 250 mg/kg-bw/day (REACH dossier; ECHA 2013b). A decrease in AGD on PND1 and a slight increase in the incidence of CRY were also observed at 50 mg/kg-bw/day and evidence of retained nipples was observed at 500 mg/kg-bw/day on PND21. It should be noted that there is uncertainty regarding this critical NOAEL as no AGD effect was observed on PND 1 in both F1 and F2 in a recent two-generation reproductive toxicity study up to 333 mg/kg-bw/day (Tyl et al. 2013). Both studies (REACH dossier; ECHA 2013b; Tyl et al. 2013) were conducted using the same strain of rat. No information was provided by Tyl et al. (2013) to explain this discrepancy. The NOAEL for maternal systemic toxicity was considered to be 50 mg/kg-bw/day based on decrease body weight gain during gestation and liver and kidney effects at 250 mg/kg-bw/day (Tyl et al. 2013).

Exposure to B79P at prepubertal-pubertal life stage

In the MCP SOS, the critical effect level for the reproductive toxicity of B79P was based on read across from closest analogues as no studies were identified for this life stage. Since the publication of the MCP SOS report, an unpublished two-generation reproductive toxicity study was submitted by industry as described above; therefore, results from the two-generation study were considered, particularly observations reported in the F1 males that were exposed in utero, through lactation to B79P and via diet until necropsy at PND126 (Tyl et al. 2013).

There were transient reductions on male body weight gain at 2500 ppm (188 mg/kg-bw/day) on PND56-63, but no effects on terminal body weights or body weight gains at the end of treatment (PND126). No effects on reproductive organ weights were observed at any dose, nor were there any histopathological findings reported. No effect on sperm counts or motility; however, a small, statistically significant increase in abnormal sperm was noted at all dose groups (19 mg/kg-bw/day and above), but there were no effects on reproductive performance of F1 males with the exception of a significantly longer precoital interval ($p < 0.05$) at the highest dose (375 mg/kg-bw/day). Changes in abnormal sperm were 1.45, 1.72, 1.96, 1.91, and 2.31% in 0, 19, 56, 188, and 375 mg/kg-bw/day, respectively, which reflect a 16% to 37% increase compared to control. The authors noted these percent abnormal sperm values were within the laboratory's historical control values for this rat strain and supplier. In addition, these values, although showing a dose-responsive nature, are also within typical ranges for untreated males of this strain in other laboratories (Kato et al. 2006; Matsumoto et al. 2008).

Systemic effects were limited to statistically significant increases in relative liver weights at 56 mg/kg-bw/day and 375 mg/kg-bw/day, but not at 188 mg/kg-bw/day with no histopathological findings. There were no changes in absolute or relative adrenal glands, but observations of small, increased incidences of bilateral cortical vacuolation at the highest dose tested (375 mg/kg-bw/day; 9 males).

There were no differences in offspring lactational parameters. There were no differences in F1 litter parameters on PND 0-4. No differences were observed in AGD across groups. No differences were observed in acquisition of PPS in F1 males.

Overall, the NOEL for the reproductive toxicity of B79P at the prepubertal-pubertal life stage was 375 mg/kg-bw/day since no adverse health effects were observed at the highest dose level tested in F1 males in the two-generation study by Tyl et al. (2013). The lowest LOEL for systemic effects was 375 mg/kg-bw/day based on small, increased incidences of bilateral cortical vacuolation in adrenal glands in the same above cohort.

Oral exposure to B79P at the mature male adult stage

In the MCP SOS, the critical effect level for the reproductive toxicity of B79P was based on read-across from closest analogues as no studies were identified for this life stage. One industry-submitted two-generation study was available after the literature cut-off date of the MCP SOS.

Reproductive effects from a 14-week exposure of adult F0 males to B79P in diet from the two-generation study described in the section above showed no adverse effects in fertility or reproductive organs (Tyl et al. 2013). A small, statistically significant increase in abnormal sperm was noted at 56 mg/kg-bw/day and above, but there were no effects on sperm count, sperm motility or reproductive performance of F0 males (Table 9-25). Changes in abnormal sperm were 1.35, 1.59, 1.73, 1.95, and 2.16% in 0, 19, 56, 188, and 375 mg/kg, respectively, which reflect a 22% to 38% increase compared to control.

The authors noted these percent abnormal sperm values were within the laboratory’s historical control values for this rat strain and supplier. In addition, these values, although showing a dose-responsive nature, are within typical ranges for untreated males of this strain in other laboratories (Kato et al. 2006; Matsumoto et al. 2008). One male in the highest dose group (375 mg/kg-bw/day) developed a misshapen bilateral testes. There was no evidence of effects on mating, production of litters, or litter size.

Table 9-25. Reproductive effects from exposure to B79P in adult males (mg/kg-bw/day)

Strain and species; dose (mg/kg-bw/day); route; duration (reference) CAS RN	Life stage at the start of dosing (age)	Hormone levels ^a (T, S, LH)	Fertility ^b	Reproductive tract pathology ^c	Other effects ^d
SD male Rats: 0, 250, 750, 2500, 5000 ppm; F0 est. 0, 19, 56, 188, 375 (diet) 14 wks Tyl et al. (2013)	6-7 weeks	NM	56 (↑ % abnormal sperm, but no effect on reproduction)	375 (1 male with bilateral misshapen testes) no histopathological findings	1) NE (BW) 2) NE (ROW) 3) 188 (ST- ↑ absolute and relative liver weight, relative kidney weight, no histopathological findings)

^aHormone level can include quantity/production of testicular testosterone (T), serum testosterone (S), or luteinizing hormone (LH).

^bFertility parameters include: sperm number, motility, morphology, viability, stages of spermatogenesis, or reproductive success at adult stage after in utero exposure.

^cReproductive tract pathology includes: any observations based on histopathological examination of the testes such as, but not limited to, multinucleated gonocytes (MNGs), necrosis, hyperplasia, clustering of small Leydig cells, vacuolisation of Sertoli cells, decrease in Leydig cell number, an increase in Leydig cell size, focal dysgenesis, and/or seminiferous tubule atrophy.

^dOther effects include: Decreased overall body weight (BW), decreased reproductive organ weight (ROW) and systemic toxicity (ST).

NM = Not measured.

NE = No effect observed at the dose range tested. When NE is presented alone, all parameters in the footnote description were measured and no statistically significant effects were observed in the endpoints at the dose range administered.

Overall, the NOAEL for reproductive toxicity identified for B79P at the adult life stage was 375 mg/kg-bw/day since no adverse health effects were observed at the highest

dose level tested in F0 adult male rats in a two generation diet study after 14-week exposure to B79P (Tyl et al. 2013).

Reproductive developmental effects: Oral exposure to B79P in females

In a previously described two-generation study by Tyl et al. (2013), F0 females exhibited a significant increase in absolute and relative liver weights at both 167 and 333 mg/kg-bw/day. There were no differences in maternal or offspring lactational parameters and no differences in F1 litter parameters on PND 0-4. For F1 females, there were no differences in body weight at acquisition of vaginal patency; reproductive performance, fertility and fecundity were equivalent across all groups. There was no evidence of effects upon evidence of mating, production of litters of litter size for the production of F2 offspring. At weaning and termination of the F2 pups on PND 21, F1 females had equivalent vaginal cytology parameters and body weights. Absolute and relative liver weights were increased at 167 and 333 mg/kg-bw/day.

Table 9-26 provides a summary of critical effects for the reproductive and/or developmental effects of B79P which will be used for risk characterization.

Table 9-26. Summary of critical effects levels for reproductive and/or developmental effects after oral exposure to B79P

Life stage during which exposure occurred	Species	Effects	LOAEL (mg/kg-bw/day)	NOAEL (mg/kg-bw/day)	Reference
In utero (GD6–21)	Rat	↓AGD, ↑ epispadis	250	50	ECHA 2013a
(Pre)pubertal	Rat	No adverse effects at the highest dose level tested	N/A	375	Tyl et al. 2013
Adult	Rat	No adverse effects at the highest dose level tested	N/A	375	Tyl et al. 2013

N/A = Not applicable

For systemic effects, critical effect levels were based on its analogue DINP, as previously described in MCP SOS (Environment Canada, Health Canada 2015b) (Table 9-27).

Table 9-27. Summary table of critical systemic effects after oral exposure to B79P

Endpoint	Species	Effect	LOAEL (mg/kg-bw/day)	NOAEL (mg/kg-bw/day)	Reference
Chronic	Rat (DINP)	Increase in absolute and relative liver and kidney weight with increase in histopathological changes in both organs in both male and females	152-184	15-18	Lington et al. 1997

DINP

The DINP SOS (Environment Canada, Health Canada 2015c) summarizes the health effects literature related to DINP. Since the publication of the DINP SOS report, a recent developmental study was identified (Table 9-28). Li et al. (2015b) examined the effects of in utero DINP exposure on offspring development. Rats were exposed to 0, 10, 100, 500 or 1000 mg/kg-bw/day DINP during GD12-21. No maternal toxicity was observed except in one dam at the highest dose level, which died on GD21.5.

Testicular pathological changes in Leydig cells (clusters) were first observed at 10 mg/kg-bw/day and MNGs were observed starting from 100 mg/kg-bw/day. The LOEL of 10 mg/kg-bw/day of this study is lower than the lowest NOAEL (50 mg/kg-bw/day) and LOAEL (159-395 mg/kg-bw/day) (Waterman et al. 2000; Clewell 2011 cited in ECHA 2013; Clewell et al. 2013) identified in the DINP SOS (Environment Canada, Health Canada 2015c). The NOAEL of 50 mg/kg-bw/day was also established by multiple agencies on the basis of the same studies (AGDH 2012; ECHA 2013b; US CPSC CHAP 2014). It should be noted that similar MNGs and Leydig cell clusters effects were observed in Clewell (2011a, 2013) at 250 mg/kg-bw/day and above. At higher dose levels, other RPS-related parameters include decreased serum testosterone levels, decreased AGD, NR, effects in sperm and other histopathological effects in the testes were observed.

Overall, the lowest LOEL identified for developmental toxicity was 10 mg/kg-bw/day based on testicular pathological changes (i.e., MNGs and Leydig cell clusters) observed at the next dose level of 100 mg/kg-bw/day (Li et al. 2015b).

Table 9-28. Effects from gestational exposure to DINP in male offspring (mg/kg-bw/day)

Strain and species; dose (mg/kg-bw/day); route; duration (reference) CAS RN	Testosterone levels^a (T, S)	Feminization parameters^b	Reproductive tract malformations and/or fertility^c	Other developmental parameters^d	Maternal effects
DINP SD rats; 0, 10, 100, 500, 1000; gavage; GD12-21 (Li et al. 2015b)	1000 (T) NM (S)	NE ^f (AGD) (NR) (PPS)	NM (CRY) NM (HYP) 100 ^f (TP-focal testis dysgenesis, MNGs, ↑ clusters of Leydig cells @ 10) NM (FER)	10 ^e , NDR (BW) (ROW) NE (FV) NM (EMB) NM (ESV)	NE (except 1/6 dam @ 1000 died at GD21.5 with all fetuses alive obtained through surgery)

^aTestosterone levels measured (can include quantity/production) at varying days post-birth. T=Testicular testosterone; S=Serum testosterone.

^bFeminization parameters can include anogenital distance (AGD), nipple retention (NR), preputial separation (PPS).

^cMalformations include: cryptorchidism (CRY), hypospadias (HYP), testicular pathology (TP), including multinucleated gonocytes (MNG), and/or reproductive effects such as fertility (FER) in offspring (sperm number, motility) or reproductive success at adult stage after in utero exposure.

^dOther developmental effects include: decreases in overall fetal body weight (BW), decreases in reproductive organ weight (ROW), fetal viability (FV), embryotoxicity (EMB), or on the incidence of external, skeletal or visceral malformations (ESV).

^e Lowest dose measured in the study.

^f Absolute AGD and AGD adjusted with cube root of pup weight were reported. Frequency of large cell clusters (i.e., >16 cells per cluster) was significantly increased from control (0.16%) to 6%, 11%, 14% and 14% in the 10, 100, 500 and 1000 mg/ kg bw/day groups, respectively (Li et al. 2015b).

NM = Not measured.

NE = No effect observed at the dose range tested. When NE is presented alone, all parameters in the footnote description were measured and no statistically significant effects were observed in the endpoints at the dose range administered.

Table 9-29 provides critical endpoints and corresponding NOAEL and/or LOAEL values for DINP which will be used for risk characterization for reproductive and developmental endpoint.

Table 9-29. Summary of critical effect levels for reproductive and/or developmental effects after oral exposure to DINP

Life Stage	Species	Effects	LOAEL (mg/kg-bw/day)	NOAEL (mg/kg-bw/day)	Reference
In utero	Rat	↑ MNGs, ↑ Leydig cell clusters/aggregation	100	10 (LOEL)	Li et al. 2015b
(Pre)pubertal	Rat (castrated)	Decreased absolute seminal vesicle and LABC weights	500 (LOEL)	100 (NOEL)	Lee and Koo 2007
Adult	Rat	Reduced relative and	742	276	Moore

		absolute reproductive organ weights	(LOEL)		1998
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For other health effects, two neurotoxicity studies were identified (Table 9-30). Table 9-31 provide critical endpoints and corresponding NOAEL and/or LOAEL value for DINP which will be used for risk characterization for systemic effects.

Table 9-30. Summary of new studies identified since the publication of DINP SOS report

Endpoint	Study details	Results	Reference
Neurotoxicity	Species/strain: male Kuming mouse Route: oral Dose and duration: 0, 1.5, 15 or 150 mg/kg-bw/day (n = 10/dose)	LOAEL = 150 mg/kg bw/ day based on reduced body weight gain, impaired cognitive ability in Morris water maze (MWM) test, histological alterations in pyramidal cells in the hippocampus	Peng 2015
Neurotoxicity	Species/strain: male Kuming mouse Route: oral Dose and duration: 0, 0.2, 2, 200 or 200 mg/kg-bw/day (n = 7/dose)	LOAEL = 20 mg/kg bw/ day based on histopathological alterations in pyramidal cells in the hippocampus, oxidative stress and inflammation in the brain. Impaired cognitive ability was observed in MWM test and anxiety in Open field test at the 200 mg/kg-bw/day.	Ma et al. 2015

Table 9-31. Summary table of critical non-cancer effects after oral exposure to DINP

Endpoint	Species	Effect	LOAEL (mg/kg-bw/day)	NOAEL (mg/kg-bw/day)	Reference
Chronic	Rat (2 years)	Increase in liver and kidney weights, increased peroxisomal enzyme levels and histological changes in both organs	152-184	15-18	Lington et al. 1997

CHIBP, BCHP and BIOP

As described in the MCP SOS (Environment Canada, Health Canada 2015b), no studies examining the potential reproductive/developmental health effects of CHIBP, BCHP and BIOP were identified. An updated literature search conducted after the literature cut-off date of the MCP SOS did not identify any new studies. As described in the exposure assessment, general population exposure to CHIBP, BCHP and BIOP from environmental media and products used by consumers is expected to be negligible. Therefore, risk to human health for this substance is not expected.

Evidence in humans

A literature update was conducted to identify any recent human data for medium-chain phthalates since the publication of the MCP SOS report. The search was focused on reproductive and developmental endpoints in males as these endpoints were identified as critical health endpoints in the SOS reports. Studies were further evaluated and scored for quality using a consistent evaluation metric (Downs and Black 1998). For the health outcomes evaluated (i.e., sex hormone levels, AGD, birth measures, male infant genitalia, preterm birth and gestational age, altered male puberty, gynecomastia, changes in semen parameters, pregnancy loss, and altered time to pregnancy), there was limited evidence of association between DINP and sex hormone levels (Main et al. 2006; Joensen et al. 2012; Mouritsen et al. 2013; Meeker and Ferguson 2014; Specht et al. 2014; Axelsson et al. 2015a; Jensen et al. 2015; Lenters et al. 2015a; Pan et al. 2015) or semen parameters (Joensen et al. 2012; Jurewicz et al. 2013; Specht et al. 2014; Axelsson et al. 2015a; Lenters et al. 2015a; Pan et al. 2015). There was inadequate evidence or no evidence of association for the other medium-chain phthalates in the Phthalate Substance Grouping and the outcomes (Table 9-32). More detail is provided in Health Canada (2016a).

Table 9-32. Summary of levels of evidence of associations between medium-chain phthalates in the Phthalate Substance Grouping and health outcomes

Outcome	DIBP (MIBP)	DCHP (MCHP)	DINP (MINP/MCOP, etc.)
Sex hormone levels	IA (4)	NM	LA (9)
Anogenital distance	NA (2)	NM	IA (2)
Birth measures	NA (3)	NM	NA (2)
Male infant genitalia	NM	NM	NA (2)
Preterm birth and gestational age	NA (2)	NM	NA (1)
Altered male puberty	IA (1)	NM	NM
Gynecomastia	NA (1)	NM	NA (1)
Changes in semen parameters	IA (3)	NM	LA (6)
Pregnancy loss	IA (3)	NM	NA (1)
Altered time to pregnancy	NA (1)	NA (1)	NA (1)

() = Number of studies

NM = Not measured in studies of quartile 2 and above (See Health Canada [2016a] for more details).

NA = No evidence of association.

IA = Inadequate evidence of an association.

LA = Limited evidence of an association.

MIBP = mono-iso-butyl phthalate

MINP = monoisononyl phthalate

9.2.2.2 Additional phthalates

As previously discussed in the cumulative risk assessment (CRA) approach document (Environment Canada, Health Canada 2015e), additional phthalates identified to have common adverse effects within the RPS as a result of alterations will be considered to be included into the CRA. After both the exposure (see section 6.1) and hazard filters were considered, BBP, DBP, DEHP, DnHP and DIOP were included in the CRA. Reproductive and development effects in males (i.e., RPS-related parameters) of these five additional phthalates were evaluated and summarized in the following sections. The RPS-related parameters were previously described in detail in the MCP SOS (Environment Canada, Health Canada 2015b).

BBP

The MCP SOS (Environment Canada, Health Canada 2015b) summarizes the reproductive and development effects of BBP in section 9.2.8.1, as BBP was identified as an analogue to B84P. Since the literature cut-off date of the MCP SOS, a recent developmental study was identified. Ahmad et al. (2014) examined the effects of in utero BBP exposure on offspring development (Table 9-33). Significant decrease in fetal body weight was observed at 4 to 20 mg/kg-bw/day during development from PND1 to 75. However, the percentage decrease in body weight was 2.5% to 5% compared to untreated control animals. Maternal effects were observed at 4 to 20 mg/kg-bw/day with decrease in maternal body weight and increase in gestation length. RPS effects were observed at 100 mg/kg-bw/day with decrease in serum testosterone level, sperm effects and decrease in reproductive organ weights.

Table 9-33. Effects from gestational exposure to BBP in male offspring (mg/kg-bw/day)

Strain and species; dose (mg/kg-bw/day); route; duration (reference)	Testosterone levels^a (T, S)	Feminization parameters^b	Reproductive tract malformations and/or fertility^c	Other developmental parameters^d	Maternal effects
Albino rats; 0 (untreated), 4, 20, 100; oral; GD14-parturition (up to GD23.5) (Ahmad et al. 2014 ^f)	NM (T) 100 (S)	NE (AGD) NM (NR) NM (PPS)	NE (CRY) NM (HYP) NM (TP) 100 (FER-↓ sperm count, ↓ sperm motility, ↑ abnormal sperm)	4 ^{e,†} (BW on PND1 and PND21, 20 on PND75) 100 (ROW- others- epididymis, prostate) NE (FV) NM (EMB) NM (ESV)	20 ^f (BW) 4 ^e (↑ gestation length)

^aTestosterone levels measured (can include quantity/production) at varying days post-birth. T=Testicular testosterone; S=Serum testosterone.

^bFeminization parameters can include anogenital distance (AGD), nipple retention (NR), preputial separation (PPS).

^cMalformations include: cryptorchidism (CRY), hypospadias (HYP), testicular pathology (TP), including multinucleated gonocytes (MNG), and/or reproductive effects such as fertility (FER) in offspring (sperm number, motility) or reproductive success at adult stage after in utero exposure.

^dOther developmental effects include: decreases in overall fetal body weight (BW), decreases in reproductive organ weight (ROW), fetal viability (FV), embryotoxicity (EMB), or on the incidence of external, skeletal or visceral malformations (ESV).

^e Lowest dose measured in the study.

^f Results were based on statistical analysis compared with untreated control. The study also presented data of vehicle control and positive control. Maternal effects were only presented in graphical format in the study (Ahmad et al. 2014).

NE = No effect observed at the dose range tested.

NM = Not measured.

Table 9-34 summarizes the critical endpoints and corresponding NOAEL and/or LOAEL values for BBP which will be used for risk characterization.

Table 9-34. Summary of critical effect levels for reproductive and or developmental effects after oral exposure to BBP

Life stage	Species	Effects	LOAEL (mg/kg-bw/day)	NOAEL (mg/kg-bw/day)	Reference
In utero	Rat	Decreased body weight (F1/F2 males and females) and ↓AGD at birth in F2 males ^a ; ↓ testicular testosterone	100	50	Aso et al. 2005; Nagao et al. 2000; Furr et al. 2014
(Pre) pubertal	Rat	↓ sperm counts (20%) and sperm	500 (LOEL)	N/A	Kwack et al. 2009

		motility			
Adult	Rat	reduced absolute epididymal weight, hyperplasia of the Leydig cells in the testes and decreased spermatozoa in the lumina of the epididymis	400	200	Aso et al. 2005; NTP 1997

^a A statistically significant increase of AGD in F1 and decreased pup weight on PND0 in F2 female offspring at 100 mg/kg-bw/day and above was also reported
 N/A = Not applicable

DBP

Early development: in utero exposure

The European Commission classified DBP as a Category 1B reproductive toxicant (presumed human reproductive toxicant) as defined in the EU regulation on classification, labelling and packaging of substances and mixtures (ECHA 2015a).

A literature search identified many studies examining the toxicity of DBP during gestation in rodents. For the purposes of characterizing effects during early male development, only studies in which effects of DBP were observed at doses below 250 mg/kg-bw/day in rats and 500 mg/kg-bw/day in mice following in utero exposure during the masculinization programming window are reported here. Summaries of the studies are described below and in Table 9-35.

Overall, adverse effects in the parameters used to describe RPS in male rat offspring after in utero exposure to DBP include decreased testicular testosterone levels, delayed PPS, decreased AGD, NR, CRY, gross and testicular malformations, and effects on fertility.

A search of the available literature revealed nine studies examining the effects of gestational exposure of DBP during the masculinization programming window in mice. The majority did not examine the parameters used to describe RPS, with only two reporting any testicular pathology and one examining testicular testosterone levels (Marsman 1995; Gaido et al. 2007, Saffarini et al. 2012).

The reproductive-developmental effects of DBP do not appear to be restricted to rodents, as one study was identified in rabbits exhibiting testicular pathological changes and sperm effects (Higuchi et al. 2003). A full summary of the health effects associated with gestational exposure to DBP is summarized in Health Canada 2016b. Table 9-35 presents a list of key studies with effects from gestational exposure to DBP in male offspring.

Table 9-35. Key studies with effects from gestational exposure to DBP in male offspring (mg/kg-bw/day)

Strain and species; dose (mg/kg-bw/day); route; duration (reference)	Testosterone levels ^a (T, S)	Feminization parameters ^b	Reproductive tract malformations and/or fertility ^c	Other developmental parameters ^d	Maternal effects
Albino rats; 0 (untreated), 2, 10, 50 DBP; oral; GD14-parturition (up to GD23.5) (Ahmad et al. 2014 ^e)	NM (T) NE (S)	NE (AGD) NM (NR) NM (PPS)	NE (CRY) NM (HYP) NM (TP) 50 (FER- ↓ sperm count, ↓ sperm motility, ↑ abnormal sperm)	10 (BW-sig. but <5%) 50 (ROW) NE (FV) NM (EMB) NM (ESV)	2 ^e (↓BW, ↑ gestational length)
SD rats; 0, 0.1, 1, 10, 50, 100 DBP; gavage; GD12-19 (Lehmann et al. 2004)	50 (T) NM (S)	NM	NM	NR (BW) NM (ROW) NM (FV) NM (EMB) NM (ESV)	NR
CD(SD)IGS rats; 0, 20, 200, 2000, 10000 ppm, est. 0, 1.5-3, 14-29, 148-291, 712-1372 based on AGDH (2008) DBP; diet; GD15-21 (Lee et al. 2004)	NM	712-1372 (AGD) 712-1372 ^f (NR) NE (PPS)	NM (CRY) NM (HYP) 148-291 (TP TP- loss of germ cell development, aggregated foci of Leydig cells) 1.5-29 (FER-sig. ↑ incidence; 148-291 sig. ↑ severity of reduced spermatocyte development)	712-1372 ^{NS} (BW) 712-1372 (ROW) NE (FV) NM (EMB) NM (ESV)	LOEL= 712-1372 (↓ BW)
SD rats; 0.1, 1, 10, 30, 50, 100, 500 DBP; gavage; GD12-21 (Boekelheide	NM	NM	NM (CRY) NM (HYP) 50, 30 (TP) A. Disorganized seminif. tubules,	NM	NM

Strain and species; dose (mg/kg-bw/day); route; duration (reference)	Testosterone levels ^a (T, S)	Feminization parameters ^b	Reproductive tract malformations and/or fertility ^c	Other developmental parameters ^d	Maternal effects
et al. 2009)			B. Cell number within testes NM (FER)		
SD rats; 0, 0.1, 0.5, 1%, est. F1 [Task 4] 0, 52, 256, 509 DBP; diet; “second generation fertility” (F2 pup results) (Wine et al. 1997)	NM	NM	NM	256 (BW) 509 (ROW) 509 (FV) 509 (EMB) NM (ESV)	LOEL= 509 (↓ body weight at wk 17)
Dutch-belted rabbits; 0, 400 DBP; gavage; GD15-29 (Higuchi et al. 2003)	NM (T) 400 ^g (↓S at 6 weeks only)	NM	400 ^{g, NS} (CRY-1/17 rabbits) 400 ^{g, NS} (HYP-1/17 rabbits) 400 ^g (TP-germinal epithelium loss, semini. epithelium with desquamation or focal vacuolation) 400 ^f (FER-sperm concentration and morphology)	NE (BW) 400 (ROW- at 12 weeks) NM (FV) NM (EMB) NM (ESV)	NM

^a Testosterone levels measured (can include quantity/production) at varying days post-birth. T=Testicular testosterone; S=Serum testosterone.

^b Feminization parameters can include anogenital distance (AGD), nipple retention (NR), preputial separation (PPS).

^c Malformations include: cryptorchidism (CRY), hypospadias (HYP), testicular pathology (TP), and/or reproductive effects such as fertility (FER) in offspring (sperm number, motility) or reproductive success at adult stage after in utero exposure.

^d Other developmental effects include: decreases in overall fetal body weight at PND 1 (BW), decreases in reproductive organ weight (ROW), embryotoxicity (EMB), fetal viability (FV), or on the incidence of external, skeletal or visceral malformations (ESV).

^e Results were based on statistical analysis compared with untreated control. The study also presented data of vehicle control and positive control. Maternal effects were only presented in graphical format in the study (Ahmad et al. 2014).

^f Nipple retention was observed as follows: Number of animals identified (%) were 0, 4, 13, 15, and 100 in controls, 20, 200, 2000, and 10,000 ppm groups (Lee et al. 2004).

^g Lowest dose measured in the study.

NE = No effect observed at the dose range tested. When NE is presented alone in the first 4 columns of effects, all parameters in the footnote description were measured and no statistically significant effects were observed in the endpoints at the dose range administered.

NM = Not measured.

NR = Results not recorded (but measurement was stated in the methods and materials).

NS = Not statistically significant.

Overall, the highest NOAEL identified for developmental toxicity of DBP after gestational exposure was 10 mg/kg-bw/day based on effects on fertility (decreased sperm count and motility and increase levels of abnormal sperm) (Ahmad et al. 2014) and a decrease in male offspring testicular testosterone levels at birth at the next dose of 50 mg/kg-bw/day (Lehmann et al. 2004). This NOAEL is supported by evidence from other studies observing decreases in both the tubular and interstitial cell populations and altered seminiferous tubule morphometry along with other mild effects on spermatocyte development at similar dose levels (Lee et al. 2004; Boekelheide et al. 2009). At lower doses, there was a slight reduction in spermatocyte development (1.5-3 mg/kg-bw/day dose range); however, the severity of this effect at this dose was minimal to slight and only minimal at the second higher dose of 14-19 mg/kg-bw/day (Lee et al. 2004). The lowest LOEL for maternal toxicity of DBP was 509 mg/kg-bw/day based on reductions in body weight gain (less than 10%) in exposed dams (Wine et al. 1997). One study in rabbits indicates that DBP has also effects in other species, but it is unknown if these effects would occur at lower doses (Higuchi et al. 2003).

Exposure at prepubertal/pubertal life stages

A literature search identified many studies examining the reproductive toxicity of DBP in young rodents. For the purposes of brevity, only studies where effects of DBP were observed at doses below 500 mg/kg-bw/day in rodents were evaluated in this screening assessment.

Overall, adverse effects in reproductive parameters observed in (pre)pubertal males after short-term exposure to DBP include changes in serum and testicular testosterone levels, histopathological effects in the testes, and potential effects in fertility (spermatogenesis, sperm motility, and number). The majority of studies available used the rat as a model for evaluation, but only within a relatively high dose range (250 to 1000 mg/kg-bw/day) which limits the interpretation of the potential reproductive toxicity of DBP in this species. One study conducted in mice examined effects at lower dose levels and reported RPS effects at dose levels lower than those in rats (Moody et al. 2013). One study was conducted in rabbits reporting evidence of testicular pathology (Higuchi et al. 2003). A full summary of the health effects associated with prepubertal/pubertal exposure to DBP is summarized in Health Canada (2016b). Table 9-36 presents a list of key studies with effects from prepubertal/pubertal exposure to DBP in males.

Table 9-36. Key studies with effects from exposure to DBP in prepubertal/pubertal males (mg/kg-bw/day)

Strain and species; dose (mg/kg-bw/day); route; duration (reference)	Life stage at the start of study (age)	Hormone levels ^a (T, S, LH)	Fertility ^b	Reproductive tract pathology ^c	Other effects ^d
C57BL/6 mice; 0, 1, 10, 50, 100, 250, 500 DBP; gavage; PND 4-14, 10 days (Moody et al. 2013)	Prepuberta I (PND 4)	NM (T) 500 (S) NM (LH) 500 (FSH)	10 (delayed spermatogenesis)	100 (↑ immature Sertoli cell and disorganization) 1 ^{e, f} (AGD relative to trunk length; 50 ^{NDR} abs AGD; 500 AGD relative to BW @ PND14)	NE (BW) 50 (ROW) NP (ST)
Wistar rats; 0, 250, 500, 1000 DBP; gavage; 15 days (Srivastava et al. 1990a)	Prepuberta I (PND 35)	NM	250 ^{e, g} (defective spermatogenesis)	250 ^{e, g} (shrunken tubules)	500 (BW) 500 (ROW) NM (ST)
SD rats; 0, 250, 500, 1000, 2000 DBP; gavage; 30 days (Xiao-feng et al. 2009)	Prepuberta I (PND 35)	NM (T) 500 (S) 1000 (↑GC)	250 (↓ spermatogenic cells, b/c of ↓LC no)	250 (↓LC number); 500 (histopathological changes in the testes)	NP (BW) 500 (ROW) NM (ST)
C57BL/6 mice; 0, 1, 10, 50, 100, 250, 500 DBP; gavage; PND4-8, 3 days (Moody et al. 2013)	Prepuberta I (PND 4)	NM	NM	100 (↑ immature Sertoli cell and disorganization)	NE (BW) 500 (ROW) 500 (ST- ↑ heart weight)
Dutch-belted rabbits; 0, 400 DBP; gavage; 15 days (Higuchi et al. 2003)	Prepuberta I (PND 28)	NM (T) NE (S) NM (LH)	400 ^e (sperm morphology defects, NE on mating behaviour)	400 ^e (TP-germinal epithelium loss, semin. epithelium with desquamation or focal vacuolation, 1/11 (CRY) NP (HYP))	NE (BW) 400 ^e (ROW- ↓ sex accessory organ at 12 weeks only) 400 ^e (ST)

Strain and species; dose (mg/kg-bw/day); route; duration (reference)	Life stage at the start of study (age)	Hormone levels ^a (T, S, LH)	Fertility ^b	Reproductive tract pathology ^c	Other effects ^d
					- ↑thyroid weight)

^a Hormone levels can include quantity/production of testicular testosterone (T), serum testosterone (S), leutinizing hormone (LH), glucocorticoid hormone (GC), or follicle stimulating hormone (FSH).

^b Fertility parameters include sperm number, motility, morphology, viability, stages of spermatogenesis, or reproductive success at adult stage after in utero exposure.

^c Reproductive tract pathology includes: testicular pathology (TP): any observations based on histopathological examination of the testes such as, but not limited to, multinucleated gonocytes/germ cells (MNGs), necrosis, hyperplasia, clustering of small Leydig cells (LC), vacuolisation of Sertoli cells, decrease in Leydig cell number, an increase in Leydig cell size, focal dysgenesis, and/or seminiferous tubule atrophy. Anogenital distance (AGD), cryptorchidism (CRY), hypospadias (HYP).

^d Other effects include: Decreased overall body weight (BW), decreased reproductive organ weight (ROW) and systemic toxicity (ST).

^e Lowest dose tested.

^f AGD results were presented in graphical format only (Moody et al. 2013).

^g Testis of rats after 250 mg/kg DBP treatment showed approximately 5% shrunken tubules with spongy appearance and defective spermatogenesis (Srivastava et al. 1990a).

NM = Not measured.

NE = No effect observed at the dose range tested. When NE is presented alone, all parameters in the footnote description were measured and no statistically significant effects were observed in the endpoints at the dose range administered.

NDR = No dose relationship.

TPr = Testosterone propionate

NP = Not reported

Overall, the lowest LOEL identified for reproductive toxicity of DBP at the prepubertal-pubertal life stage was 10-50 mg/kg-bw/day based on delayed spermatogenesis in male mice exposed to DBP for 10 days at this dose and above (Moody et al. 2013). At the next dose level of 50 mg/kg-bw/day, significant reduction in absolute AGD was observed on PND14 mice, but the effect was not significant when AGD was measured relative to body weight. An increase in immature Sertoli cell and disorganization was observed at 100 mg/kg-bw/day. No comparison can be made for rats as there were no studies available at similar dose ranges. The lowest dose tested in rats was 250 mg/kg-bw/day with observations of defective spermatogenesis, shrunken tubules, decrease in spermatogenic cells and Leydig cell numbers (Srivastava et al. 1990a; Xiao-feng et al. 2009). The lowest LOEL for systemic toxicity for mice was 500 mg/kg-bw/day based on increased relative heart weight after 3 days of DBP treatment. This effect was lost by 14 days (Moody et al. 2013). One study in rabbits indicates that DBP also effects other species, but it is unknown if these effects would occur at lower doses (Higuchi et al. 2003).

Exposure at the mature male adult stage

The MCP SOS (Environment Canada, Health Canada 2015b) summarizes the health effects of DBP in sexually mature adult rats (PND55+) as DBP was identified as an analogue to DIBP. Since the literature cut-off date of the MCP SOS (Environment

Canada, Health Canada 2015b), new literature was identified (Table 9-37). DBP (0, 200, 400 or 600 mg/kg-bw/day) was administered to rats by oral gavage for 15 days (Aly et al. 2015). At the lowest dose level of 200 mg/kg-bw/day, decrease in serum testosterone level, decrease in sperm count, and decrease in sperm motility were observed. In addition, histopathological examination of the testes indicated degeneration with absence of spermatogenic series in the lumen of some seminiferous tubules starting from 200 mg/kg-bw/day. However, the results from this study are limited as systemic effect and clinical signs of the animals were not measured. In another study, adverse effects (testicular pathological changes and effects on sperm) were observed starting from 500 mg/kg bw/day (Nair 2015).

Table 9-37. Effects from exposure to DBP in adults males (mg/kg-bw/day)

Strain and species; dose (mg/kg-bw/day); route; duration (reference)	Life stage at the start of dosing (age)	Hormone levels^a (T, S, LH)	Fertility^b	Reproductive tract pathology^c	Other effects^d
Wistar rat; 0, 200, 400, 600; gavage; 15 days (Aly et al. 2015)	~13 weeks	NM (T) 200 ^e (↓S) NM (LH)	200 ^e (↓ sperm count, ↓ sperm motility)	200 ^e (degeneration with absence of spermatogenic series in the lumen of some seminiferous tubules)	NM (BW) 200 ^e (ROW) NM (ST)
Wistar rats; 0, 500, 1000, 1500 DBP; oral; 7 days (Nair 2015)	Adult (age not reported, 120-122 g)	NM	500 ^e (FER- ↓ sperm density, karyorrhexis in spermatocyte s,)	500 ^e (TP- atrophy of Leydig cells)	NM (BW) NM (ST) NE (ROW)

^a Hormone level can include quantity/production of testicular testosterone (T), serum testosterone (S), or leutinizing hormone (LH).

^b Fertility parameters include: sperm number, motility, morphology, viability, stages of spermatogenesis, or reproductive success after mating.

^c Reproductive tract pathology includes: any observations based on histopathological examination of the testes such as, but not limited to, multinucleated gonocytes (MNGs), necrosis, hyperplasia, clustering of small Leydig cells, vacuolisation of Sertoli cells, decrease in Leydig cell number, an increase in Leydig cell size, focal dysgenesis, and/or seminiferous tubule atrophy.

^d Other effects include: Decreased overall body weight (BW), decreased reproductive organ weight (ROW) and systemic toxicity (ST).

^e Lowest dose measured in the study.

NM = Not measured.

NE = No effect observed at the dose range tested. When NE is presented alone, all parameters in the footnote description were measured and no statistically significant effects were observed in the endpoints at the dose range administered.

Table 9-38 provides critical endpoint and corresponding NOAEL and/or LOAEL value for DBP reproductive and/or developmental effects in mature adult male rats.

Table 9-38. Summary of critical effect level for reproductive and/or developmental effects in mature adult male rats after oral exposure to DBP

Life stage	Species	Effects	LOAEL (mg/kg-bw/day)	NOAEL (mg/kg-bw/day)	Reference
Adult	Rat	Testicular pathology, effects on sperm count, density, and motility, and decreased ROW	500	250	Srivastava et al. 1990b; Zhou et al. 2011c; Nair 2015

DEHP

Early development: in utero exposure

The European Commission classified DEHP as a Category 1B reproductive toxicant (presumed human reproductive toxicant) as defined in the EU regulation on classification, labelling and packaging of substances and mixtures (ECHA 2015b).

A literature search identified many studies examining the toxicity of DEHP during gestation in rodents. For the purposes of the CRA, only studies covering the masculinization programming window where effects of DEHP were observed at doses at and below 50 mg/kg-bw/day in rats and 100 mg/kg bw/day in mice were evaluated in this draft screening assessment.

Overall, adverse effects in the parameters used to describe RPS in male rat offspring after in utero exposure to DEHP include decreased serum and testicular testosterone levels, delayed PPS, AGD, increase incidences of NR and CRY, gross testicular malformations, and effects in fertility. A full summary of the health effects associated with gestational exposure to DEHP is summarized in Health Canada (2016b). Table 9-39 presents a list of key studies with effects from gestational exposure to DEHP in male offspring.

Table 9-39. Key studies with effects from gestational exposure to DEHP in male offspring (mg/kg-bw/day)

Strain and species; dose (mg/kg-bw/day); route;	Testosterone levels ^a (T, S)	Feminization parameters ^b	Reproductive tract malformations and/or fertility ^c	Other developmental parameters ^d	Maternal effects
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duration (reference)					
<p>CrI:CD BR SD rats; 1.5 (Con), 10, 30, 100, 300, 1000, 7500, 10000 ppm (est. F0 : 0.12, 0.78, 2.4, 7.9, 23, 77, 592, 775); diet; 6 weeks prior to mating – PND35 of last of three litters (Wolfe and Layton 2003)</p>	NM	<p>592 (AGD) NE (NR) 592 (PPS)</p>	<p>592 (CRY^e) NP (HYP) 23 (TP- low incidence of small and/or aplastic epididymis and testes, small seminal vesicle, minimal seminiferous tubule atrophy; small prostate @ 77) 592 (FER- ↓ sperm measured); 775 (FER- ↓ epididymal sperm density)</p>	<p>775 (BW) 592 (ROW- in adults) 592 (FV) NM (EMB) NM (ESV)</p>	<p>LOEL= 592 (↑ absolute and relative liver weights, relative kidney weight, ↑ food consumpti on during gestation, ↓ food consumpti on during lactation)</p>
<p>CrI:CD BR SD rats; 1.5 (Con), 10, 30, 100, 300, 1000, 7500, 10000 ppm (est. F1 : 0.09, 0.48, 1.4, 4.9, 14, 48, 391,</p>	NM	<p>391 (AGD) NE (NR) 0.48 (PPS)</p>	<p>1.4 (CRY^e) NP (HYP) 14 (TP- low incidence of small and/or aplastic epididymis and testes; seminiferous tubule atrophy at 391) 4.9^{NDR} (FER- abnormal sperm morphology); 391 (FER- ↓</p>	<p>391 (BW) 391 (ROW- in adults) 543 (FV- no offspring) 543 (EMB^e) NM (ESV)</p>	<p>LOEL= 391 (↑ absolute and relative liver weights and ↑ food consumpti on)</p>

543); diet; 6 weeks prematuring – PND35 of last of three litters (Wolfe and Layton 2003)			sperm, ↓ motile percentage, ↓ epididymal sperm density)		
Crl:CD BR SD rats; 1.5 (Con), 10, 30, 100, 300, 1000, 7500 ppm (est. F2: 0.1, 0.47, 1.4, 4.8, 14, 46, 359); diet; 6 weeks prematuring – PND35 of last of three litters (Wolfe and Layton 2003)	NM	359 (AGD) 359 (NR) 359 (PPS)	359 (CRY ^e) NP (HYP) NP (TP) 359 (FER- ↓ sperm, ↓ epididymal sperm density)	NE (BW) 359 (ROW- in adults) NP (FV) 359 (EMB ^e) NM (ESV)	LOEL= 359 (↑ absolute and relative liver weights, ↑ food consumpti on)
Wistar rats; 0, 3, 10, 30, 100, 300, 600, 900; gavage; GD7- PND16	NM	10 (AGD ^f) 10 (NR ^f) NM (PPS)	NM (CRY) NM (HYP) 300 (TP- immature testes, delayed seminiferous epithelium development,	300 (BW) 10 (ROW ^f) 10 ^{NDR} (FV) NM (EMB) NM (ESV)	NE

(Christian sen et al. 2010)			focal Leydig cell hyperplasia, ↓ seminiferous tubule diameter, ↓ germ cells) NM (FER)		
Wistar rats; 0, 0.015-1.215; 5, 15, 45, 135, 405; gavage; GD6-PND21 (Andrade et al. 2006a, b)	NE (T- PND1) 0.045 ^{NDR} (↑ S)	0.015 ^e (↑), 405 (↓) (AGD-PND22) 405 (NR) 15 (PPS)	5 ^g (CRY) NE (HYP) 135 (TP- MNG, ↓ germ cell layers); 405 (TP- ↓ germ cell differentiation in seminiferous tubules, ↓ tubule diameter, ↓ lumen) 15 ^g (FER- ↓ sperm pro, 25%); 0.045 (FER- ↑ abnormalities ^{NDR})	0.045 ^{NDR} (↑ BW, PND1) 5 (↑ ROW ^g transient) NE (FV) NE (EMB) NM (ESV)	NE

^aTestosterone levels measured (can include quantity/production) at varying days post-birth. T=Testicular testosterone; S=Serum testosterone.

^bFeminization parameters can include anogenital distance (AGD), nipple retention (NR), preputial separation (PPS).

^cMalformations include: cryptorchidism (CRY), hypospadias (HYP), testicular pathology (TP), including multinucleated gonocytes (MNG), and/or reproductive effects such as fertility (FER) in offspring (sperm number, motility) or reproductive success at adult stage after in utero exposure. TTM = transabdominal testicular migration

^dOther developmental effects include: decreases in overall fetal body weight (BW), decreases in reproductive organ weight (ROW), fetal viability (FV), embryotoxicity (EMB), or on the incidence of external, skeletal or visceral malformations (ESV).

^eCRY was based on significant delay in testes descent. EMB was based on an additional crossover mating trial conducted using the 7500 and 10000 ppm males and females (Wolfe and Layton 2003).

^fthe effect levels for AGD and NR were based on 1 set out of 2 sets of experiments. Similar effects were observed at higher dose level in the other set of experiment. The effect level for ROW was based on combining the results of the 2 sets of experiments (Christiansen et al. 2010).

^gCRY was based on undescended (ectopic) testes observed in three animals, exposed to either 5, 135 and 405 mg/kg-bw/day (one case in each dose). In all three cases, undescended testes were unilateral (right side) and located in the superficial inguinal pouch. The ROW effect level reported by author was adjusted for body weight by covariance analysis (Andrade et al. 2006a,b).

NDR =No dose response relationship.

NP = Not reported.

NM = Not measured.

NE = No effect observed at the dose range tested. When NE is presented alone in the first 4 columns of effects, all parameters in the footnote description were measured and no statistically significant effects were observed in the endpoints at the dose range administered.

Overall, the highest NOAEL identified for developmental toxicity of DEHP after gestational exposure was 4.8 mg/kg-bw/day based on small and/or aplastic epididymis, testicular pathology and other RPS effects observed in F1 and F2 at the next dose level of 14 mg/kg-bw/day in a multigenerational reproductive toxicity study (Wolfe and Layton 2003; Blystone et al. 2010). This effect level was also established by other jurisdictions

(ECJRC 2008; Danish EPA 2012; US CPSC CHAP 2014; EFSA 2005). At similar dose levels of 10-15 mg/kg-bw/day, decreases in AGD, increased NR, decreased reproductive organ weights, and delayed PPS were observed in rat offspring in other studies (Andrade et al. 2006a,b; Christiansen et al. 2010). The lowest NOEL for maternal toxicity of DEHP was 359 mg/kg-bw/day based on increase in liver weight and food consumption.

Exposure at prepubertal/pubertal life stages

A literature search identified many studies examining the reproductive toxicity of DEHP in young rodents. Results from repeated-dose oral exposure studies in sexually immature rats (PND1–55) have shown that administration of DEHP can cause reproductive effects in male rats.

Overall, adverse effects observed in (pre)pubertal males after short-term exposure to DEHP include changes in serum and testicular testosterone levels, histopathological effects in the testes, and potential effects in fertility (spermatogenesis, sperm motility, and number). Reproductive effects observed in prepubertal or pubertal mice after exposure to DEHP occurred at higher doses than rats. Other species were also found to be less sensitive than rats to DEHP. No significant effects were observed in *Cynomolgus* monkeys, marmosets and Syrian hamsters treated with DEHP. A summary of the health effects associated with prepubertal/pubertal exposure to DEHP is summarized in Health Canada (2016b). Table 9-40 presents key studies with effects from prepubertal/pubertal exposure to DEHP in males.

Table 9-40. Key studies of effects from exposure to DEHP in (pre)pubertal males (mg/kg-bw/day)

Strain and species; dose (mg/kg-bw/day); route; duration (reference)	Life stage at the start of dosing (age)	Hormone levels^a (T, S, LH)	Fertility^b	Reproductive tract pathology^c	Other effects^d
SD rats; 0, 10, 100, 1000, 2000 (fatal) ; gavage; 5 days (Dostal et al. 1988)	Prepubertal (PND21)	NM (T) NM (S) NM (LH)	NM	1000 (loss of spermatocytes in Sertoli cell cytoplasm, degenerating spermatocytes)	1000 (BW-sig. @ 10, NS @ 100) 100 (ROW) NM (ST)
SD rats; 0, 200, 500, 1000; gavage; 5 days (fertility group mated at 8-15 wks (mated to F344)) (Dostal et al. 1988)	Postnatal (PND6)	NM	200 ^e (↓ spermatid heads at 13 weeks of age; @ 1000 at 19 weeks of age)	500 (↓ Sertoli cell number 24h after last dose)	1000(BW-24h after last dose) 500 (ROW-24h after last dose) NM (ST)
SD rats; 0, 300, 600; gavage; 21 days (Cammack et al. 2003)	Postnatal (PND3-5)	NM	NE (PND90)	300 (PND25; testicular changes, such as partial depletion of the germinal epithelium and/or decreased diameter of the seminiferous tubules) Less severe @PND 90	600 (BW) 300 (ROW-PND25, PND 90) 300 (ST-↑ rel. liver weight)
Wistar rats; 0, 1, 3, 10, 30, 100, 300; gavage; 40 days (Tonk et al. 2012) ^f	Prepubertal (PND10)	NM (T) 3.9(↓S – BMDL ₅) 14 (↑LH-BMDL ₅)	9.5 (sperm count) (BMDL ₅)	300 ^f (TP- lesions; sertoli cell vacuolization)	NE (BW) 84 (ROW – BMDL ₅) 4.4 (ST-↑ rel. liver weight – BMDL ₅)
Wistar rats; 0, 1, 3, 10, 30, 100, 300; gavage; 40 days (Tonk et al. 2012) ^f	Pubertal-adult (PND50)	NM (T) 3.9 (S-BMDL ₅) 62 (LH-BMDL ₅)	55 (BMDL ₅ , sperm count)	300 ^f (TP- lesions; sertoli cell vacuolization)	NE (BW) 517 (ROW BMDL ₅) 4.4 (ST-↑ rel. liver weight – BMDL ₅)

Strain and species; dose (mg/kg-bw/day); route; duration (reference)	Life stage at the start of dosing (age)	Hormone levels ^a (T, S, LH)	Fertility ^b	Reproductive tract pathology ^c	Other effects ^d
					(ST)

^a Hormone levels can include quantity/production of testicular testosterone (T), serum testosterone (S), leutinizing hormone (LH), glucocorticoid hormone (GC), or follicle stimulating hormone (FSH).

^b Fertility parameters include sperm number, motility, morphology, viability, stages of spermatogenesis, or reproductive success at adult stage after in utero exposure.

^c Reproductive tract pathology includes: testicular pathology (TP): any observations based on histopathological examination of the testes such as, but not limited to, multinucleated gonocytes/germ cells (MNGs), necrosis, hyperplasia, clustering of small Leydig cells (LC), vacuolisation of Sertoli cells, decrease in Leydig cell number, an increase in Leydig cell size, focal dysgenesis, and/or seminiferous tubule atrophy.

^d Other effects include: Decreased overall body weight (BW), decreased reproductive organ weight (ROW) and systemic toxicity (ST).

^e Lowest dose measured in the study.

^f Data were represented as 5% lower confidence bound of benchmark dose (BMDL₅). In juvenile males, preputial separation was delayed at the 300 mg/kg bw dose group. Testicular pathological changes were only examined at the 300 mg/kg-bw/day dose group (Tonk et al. 2012).

NM = Not measured.

NE = No effect observed at the dose range tested. When NE is presented alone, all parameters in the footnote description were measured and no statistically significant effects were observed in the endpoints at the dose range administered.

Overall, the highest NOAEL identified for reproductive toxicity of DEHP at the prepubertal-pubertal life stage was 10 mg/kg-bw/day based on a significant decrease in absolute testis weight at the next dose level of 100 mg/kg-bw/day in rats exposed to DEHP for 5 days from PND21 (Dostal et al. 1988). At 200 mg/kg-bw/day, a decrease in spermatid heads was observed at 13 weeks of age in rats exposed for 5 days from PND6 (Dostal et al. 1988). Testicular pathological changes were observed at 300 mg/kg-bw/day and higher in rats exposed to DEHP for 21 days from PND3-5 (Cammack et al. 2003) and rats exposed for 40 days from PND10 or PND50 (Tonk et al. 2012).

Exposure at the mature male adult stage

Studies examining the potential reproductive toxicity of DEHP at the adult male life stage (PND55+) were identified in rats, mice, marmosets and ferrets.

In rats, chronic exposure to DEHP (104 weeks to 2 years) resulted in inhibition of spermatogenesis starting from 10-29 mg/kg-bw/day (Ganning 1991; David et al. 2000a). In animals treated for less than a chronic duration (2-13 weeks), inhibition of spermatogenesis, decrease sperm count and decrease in sperm motility was observed at 300-900 mg/kg-bw/day (Poon et al. 1997; Wolfe and Layton 2003; Kwack et al. 2009; Tonk et al. 2012; Abd-Ellah et al. 2016). Decrease in testis weight and testicular pathological changes were generally observed at 300 mg/kg-bw/day and above.

Adult mice, ferrets, and marmosets were found to be less sensitive than rats to DEHP. Systemic effects in mice such as a decrease in relative kidney weight and an increase in absolute liver weight were observed at 99 mg/kg-bw/day whereas effects on sperm and testicular pathological changes were observed at 292 mg/kg-bw/day in a chronic study (David et al. 2000b). In Ferrets, testicular pathological changes, decreases in body weight and increases in liver weight were observed at a much higher dose level of 1200 mg/kg-bw/day (Lake et al. 1976). In marmoset, only peroxisome proliferator-activated receptor (PPAR) effects in liver were observed at 500 mg/kg-bw/day (Kurata et al. 1998). A summary of the health effects associated with adult life stage exposure to DEHP is summarized in Health Canada (2016b). Table 9-41 presents key study with effects from adult life stage exposure to DEHP in males.

Table 9-41. Effects from exposure to DEHP in adults males (mg/kg-bw/day)

Strain and species; dose (mg/kg-bw/day); route; duration (reference)	Life stage at the start of dosing (age)	Hormone levels^a (T, S, LH)	Fertility^b	Reproductive tract pathology^c	Other effects^d
Fischer 344 rats; 0, 100, 500, 2500, 12500 ppm (est. 0, 5.8, 28.9, 146.6, 789); diet; 104 weeks (David et al. 2000a)	6 weeks	NM (T) NM (S) NM (LH)	28.9 (↓spermatogenesis)	↓interstitial cell tumors of testes at 789	789 (BW- ↓ from wk 1) 789 (ROW) 146.6 (ST- ↑ rel/abs. kidney, liver weight, ↑ rel. lung weight; 789 – liver and kidney ^e histopath effects, pancreas, ↑pituitary castration cells) ↑spongiosis hepatitis at 146.6 and 789)

^a Hormone level can include quantity/production of testicular testosterone (T), serum testosterone (S), or leutinizing hormone (LH).

^b Fertility parameters include: sperm number, motility, morphology, viability, stages of spermatogenesis, or reproductive success after mating.

^c Reproductive tract pathology includes: any observations based on histopathological examination of the testes such as, but not limited to, multinucleated gonocytes (MNGs), necrosis, hyperplasia, clustering of small Leydig cells, vacuolisation of Sertoli cells, decrease in Leydig cell number, an increase in Leydig cell size, focal dysgenesis, and/or seminiferous tubule atrophy.

^d Other effects include: Decreased overall body weight (BW), decreased reproductive organ weight (ROW) and systemic toxicity (ST).

^e Other systemic effects include: chronic progressive nephropathy observed in all male groups with increased severity at 789 mg/kg-bw/day. Significant ↑ of hyperplasia and adenomas of pancreas in males only at 789 mg/kg-bw/day (David et al. 2000a).
 NM = Not measured.

Overall, the highest NOAEL identified for reproductive toxicity of DEHP at the adult life stage was 5.8 mg/kg-bw/day based on a decrease in spermatogenesis at the next dose level of 29 mg/kg-bw/day in male adult rats exposed chronically to DEHP for 104 weeks (David et al. 2000a).

DnHP

Early development: in utero exposure

The European Commission classified DnHP as a Category 1B reproductive toxicant (presumed human reproductive toxicant) as defined in the EU regulation on classification, labelling and packaging of substances and mixtures (ECHA 2015c).

A literature search identified a number of recent studies examining the toxicity of DnHP during gestation in rodents. For the purposes of the CRA, only studies covering the masculinization programming window in males were evaluated in this draft screening assessment.

Overall, adverse effects in the parameters used to describe RPS in male rat offspring after in utero exposure to DnHP include decreased serum and testicular testosterone levels, delayed PPS, AGD, retention of nipple/areolae (NR), increase incidences of CRY and hypospadias, gross testicular malformations, and effects in fertility. Two studies were conducted in mice where embryotoxicity and effects on fetal viability were observed. A summary of the health effects associated with gestational exposure to DnHP is summarized in Health Canada (2016b). Table 9-42 presents a list of key studies with effects from gestational exposure to DnHP in male offspring.

Table 9-42. Key studies with effects from gestational exposure to DnHP in male offspring (mg/kg-bw/day)

Strain and species; dose (mg/kg-bw/day); route; duration (reference)	Testosterone levels ^a (T, S)	Feminization parameters ^b	Reproductive tract malformations and/or fertility ^c	Other developmental parameters ^d	Maternal effects
SD rats; 0, 5, 20, 50, 100, 125, 250, 500, 625;	20 (T- ↓ by 17% on GD19; ED ₅₀ = 67.4 mg/kg) NM (S)	NM (AGD) NM (NR) NM (PPS)	NM (CRY) NM (HYP) 500 ^e (TP-abnormal distribution of	NM (BW) NM (ROW) NM (FV) NM (EMB) NM (ESV)	NP

gavage; GD12-19 (Saillenfait et al. 2013a)			Leydig cells on GD19, ↓ number of Leydig cell clusters, ↑ size of Leydig cell clusters, other effects) NM (FER)		
Wistar rats; 0, 20, 100, 500; oral gavage; GD6-19 (Ahbab and Barlas 2015)	20 ^f (↓T:450 pg/ml testosterone compared to control, p < 0.05)	20 ^f (↓AGD/cube root of body weight ratio, control at approx. 2.4 mm/g ^{1/3} and 20 mg/kg/day at approx. 2.0 mm/g ^{1/3} , p < 0.05)	NM (CRY) NM (HYP) 20 ^f (TP – atrophic and small seminiferous tubules, decreased germ cells in tubules, detached cells from tubular wall) NM (FER)	20 ^f (↓15.9% BW; at 100, ↓20.5% BW; at 500, ↑ 13.6% BW) NM (ROW) NE (FV) 20 ^f (EMB- resorption based on number of offspring, not by percentage) NM (ESV)	NE

^aTestosterone levels measured (can include quantity/production) at varying days post-birth. T=Testicular testosterone; S=Serum testosterone.

^bFeminization parameters can include anogenital distance (AGD), nipple retention (NR), preputial separation (PPS).

^cMalformations include: cryptorchidism (CRY), hypospadias (HYP), testicular pathology (TP), including multinucleated gonocytes (MNG), and/or reproductive effects such as fertility (FER) in offspring (sperm number, motility) or reproductive success at adult stage after in utero exposure. TTM = transabdominal testicular migration

^dOther developmental effects include: decreases in overall fetal body weight (BW), decreases in reproductive organ weight (ROW), fetal viability (FV), embryotoxicity (EMB), or on the incidence of external, skeletal or visceral malformations (ESV).

^e TP was only examined in the control and 500 mg/kg-bw/day dose groups (Saillenfait et al. 2013).

^f Lowest dose measured in the study.

NP = Results not recorded (but measurement was stated in the methods and materials).

NM = Not measured.

NE = No effect observed at the dose range tested. When NE is presented alone in the first 4 columns of effects, all parameters in the footnote description were measured and no statistically significant effects were observed in the endpoints at the dose range administered.

Overall, the highest NOAEL identified for developmental toxicity of DnHP after gestational exposure was 5 mg/kg-bw/day based on decreased serum or testicular testosterone levels, decreased AGD at birth in males and testicular pathological changes observed at 20 mg/kg-bw/day or higher in rats (Ahbab and Barlas 2015; Saillenfait et al. 2013a).

Exposure at prepubertal/pubertal life stages

A literature search identified four studies examining the reproductive toxicity of DnHP in young sexually immature rats (PND1–55). These studies were generally tested at high dose levels and did not describe RPS-related parameters other than one study that was tested at lower dose levels using castrated male rats. A summary of the health effects associated with prepubertal/pubertal exposure to DnHP is summarized in Health Canada (2016b). Since available studies were limited, DEHP was identified, using the same chemical categories and read-across approach as that used for other phthalates, as the “closest analogue” phthalate, taking into consideration the similarities in monoester metabolism as well as the length and nature of the ester chains (Health Canada 2015).

As described earlier in the DEHP section, the highest NOAEL identified for reproductive toxicity of DEHP at the prepubertal-pubertal life stage was 10 mg/kg-bw/day based on significant decreases in absolute testis weight at the next dose level of 100 mg/kg-bw/day in rats exposed to DEHP for 5 days from PND21 (Dostal et al. 1988). Therefore, the critical effect level of 10 mg/kg-bw/day will be used to characterize the risk of developmental toxicity of DnHP for this life stage.

Exposure at the mature male adult stage

Two studies examining the potential reproductive toxicity of DnHP at the adult male life stage (PND55+) were identified in rodents. One study was conducted in rats where RPS-related parameters were not measured. Another study was conducted in mice where fertility effects and testicular pathology were examined. A summary of the health effects associated with adult stage exposure to DnHP is summarized in Health Canada (2016b). Table 9-43 presents the key study with effects from exposure to DnHP in adult males.

Table 9-43. Effects from exposure to DnHP in mature adult males (mg/kg-bw/day)

Strain and species; dose (mg/kg-bw/day); route; duration (reference)	Age at the start of dosing	Hormone levels^a (T, S, LH)	Fertility^b	Reproductive tract pathology^c	Other effects^d
COBS Cr1 : CD-1, (IRC)BR outbred albino mice;	PND 42	NM	390 ^e (↓fertility at mating, litters/pair, live pups/litter, proportion of	1560 ^f (extensive atrophy of seminiferous tubules, tubules were lined mostly	1560 ^f (↓10.27% BW in F ₀ male, calculated

Strain and species; dose (mg/kg-bw/day); route; duration (reference)	Age at the start of dosing	Hormone levels ^a (T, S, LH)	Fertility ^b	Reproductive tract pathology ^c	Other effects ^d
0, 0.3, 0.6, 1.2%; est. 0, 390, 780, 1560 (based on dose conversion by HC 1994); (crossover mating trial and necropsy of highest dose only); oral diet; 7 days pre-mating and 98 days cohabitation (total 105 days exposure) (Lamb et al. 1987)			pups born alive, live pup weight; 780, produced 1 litter; 1560, infertile) 1560 ^f (sperm parameters, ↓ % motile sperm, sperm concentration, % abnormal sperm)	by Sertoli cells, no normal spermatogenesis observed, in 3 of 18 mice, observed microscopic changes in seminal vesicles	from 36.19g at 1560 dose compared to 40.33 for control) 1560 ^f (↓ ROW, i.e. left testis and epididymis, right testis, right epididymis, prostate, seminal vesicles) 1560 (ST-↓ liver, kidney and adrenal weight)

^aHormone levels can include quantity/production of testicular testosterone (T), serum testosterone (S), or leutinizing hormone (LH).

^bFertility parameters include sperm number, motility, morphology, viability, stages of spermatogenesis, or reproductive success after mating.

^cReproductive tract pathology includes: any observations based on histopathological examination of the testes such as, but not limited to, multinucleated gonocytes (MNGs), necrosis, hyperplasia, clustering of small Leydig cells, vacuolisation of Sertoli cells, decrease in Leydig cell number, an increase in Leydig cell size, focal dysgenesis, and/or seminiferous tubule atrophy.

^dOther effects include: Decreased overall body weight (BW), decreased reproductive organ weight (ROW) and systemic toxicity (ST).

^eLowest dose tested.

^fReproductive tract pathology, BW and ROW parameters were only examined in the control and the 1560 mg/kg-bw/day dose groups (Lamb et al. 1987).

NM = Not measured.

Overall, no NOAEL was identified and the lowest LOAEL identified for reproductive

toxicity of DnHP was 390 mg/kg-bw/day in mice based on adverse effects in fertility (decreases in fertility, the number of litters per pair, the number of live pups per litter and the proportion of pups born alive) treated with DnHP for 105 days during the adult male life stage (Lamb et al. 1987).

DIOP

Early development: in utero exposure

The European Commission classified DIOP as a Category 1B reproductive toxicant (presumed human reproductive toxicant) as defined in the EU regulation on classification, labelling and packaging of substances and mixtures (ECHA 2015d).

Three studies were identified that were all conducted by Saillenfait et al. (2013b) during the masculinization programming window. Adverse effects in the parameters used to describe RPS in male rat offspring after in utero exposure to DIOP included decreased testicular testosterone levels, decreased AGD, increased incidence of NR and CRY, gross testicular malformations, and effects in fertility. A summary of the health effects associated with gestational exposure to DIOP is summarized in Health Canada (2016b). Table 9-44 presents the key study with effects from gestational exposure to DnHP in male offspring.

Table 9-44. Effects from gestational exposure to DIOP in male offspring (mg/kg-bw/day)

Strain and species; dose (mg/kg-bw/day); route; duration (reference)	Testosterone levels ^a (T, S)	Feminization parameters ^b	Reproductive tract malformations and/or fertility ^c	Other developmental parameters ^d	Maternal effects
<p>DIOP</p> <p>SD Rats; 0, 100, 500, 1000; gavage; GD12-21</p> <p>(Saillenfait et al. 2013b)</p>	<p>NM</p>	<p>NM (AGD) 1000 (NR @ PND 68-84) NM (PPS)</p>	<p>1000 (CRY @ PND 68-84) 1000 (HYP @ PND 68-84) 500 (TP-one incidence each of unilaterally enlarged testis, abnormal epididymis, underdeveloped seminal vesicles and</p>	<p>NE (BW) 500 (ROW) 1000 (FV @PND21) NE (EMB) NM (ESV)</p>	<p>1000 (BW)</p>

			prostate) 500 (FER- hypospermato genesis)		
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^a Testosterone levels measured (can include quantity/production) at varying days post-birth. T=Testicular testosterone; S=Serum testosterone.

^b Feminization parameters can include anogenital distance (AGD), nipple retention (NR), preputial separation (PPS).

^c Malformations can include cryptorchidism (CRY), hypospadias (HYP), testicular pathology (TP), and/or reproductive effects such as fertility (FER) in offspring (sperm number, motility) or reproductive success at adult stage after in utero exposure. TTM = transabdominal testicular migration.

^d Other developmental effects include decreases in overall fetal body weight at PND 1 (BW), decreases in reproductive organ weight (ROW), embryo/fetal viability (FV), average litter size (ALS), or on the incidence of external, skeletal or visceral malformations (ESV).

NM = Not measured.

NE = No effect observed at the dose range tested. When NE is presented alone in the first 4 columns, all parameters in the footnote description were measured and no statistically significant effects were observed in the endpoints at the dose range administered.

Overall, the highest NOAEL identified for developmental toxicity of DIOP after gestational exposure was 100 mg/kg-bw/day based on testicular pathological changes, effects on fertility and decreased testis weight at the next dose level of 500 mg/kg-bw/day. Maternal decrease in body weight was observed at 1000 mg/kg-bw/day (Saillenfait et al. 2013b).

Exposure at prepubertal/pubertal life stages

There were no repeated-dose oral exposure studies in sexually immature animals (PND1-55) with DIOP. DIHepP was identified as the appropriate analogue to use for read across. The MCP SOS (Environment Canada, Health Canada 2015b) summarizes the health effects literature related to DIHepP. Table 9-45 provides the critical endpoints and corresponding NOAEL and/or LOAEL values for DIOP.

Table 9-45. Summary of critical effect levels for reproductive and/or developmental effects after oral exposure to DIOP based on its analogue

Life stage	Species	Effects	LOAEL (mg/kg-bw/day)	NOAEL (mg/kg-bw/day)	Reference
(pre)pubertal	Rat (DIHepP)	Significant reduction in AGD; delayed preputial separation, nipple retention, hypospadias and cryptorchidism in F1 pups	419–764	227–416	McKee et al. 2006
adult	Rat (DIHepP)	No adverse effects observed up to the highest dose level tested	NA	404–623	McKee et al. 2006

NA = Not applicable

Oral exposure at the mature male adult stage

There were no repeated-dose oral exposure studies in adult animals with DIOP. DIHepP was identified as the appropriate analogue to use for read across. The MCP SOS (Environment Canada, Health Canada 2015b) summarizes the health effects literature related to DIHepP. Table 9-45, described in the above section, provides the critical endpoints and corresponding NOAEL and/or LOAEL values for DIOP.

Evidence in humans

A literature search was conducted to identify any human data for additional phthalates. The search was focused on reproductive and developmental endpoints in males as these endpoints were identified as critical health endpoints in the SOS reports. Studies were further evaluated and scored for quality using a consistent evaluation metric (Downs and Black 1998).

For the health outcomes evaluated (i.e., sex hormone levels, anogenital distance, birth measures, male infant genitalia, preterm birth and gestational age, altered male puberty, gynecomastia, changes in semen parameters, pregnancy loss, and altered time to pregnancy), there was limited evidence of association between DEHP and sex hormone levels (Pan et al. 2006; Meeker et al. 2009; Li et al. 2011; Mendiola et al. 2011, 2012; Joensen et al. 2012; Araki et al. 2014; Ferguson et al. 2014a; Pant et al. 2014; Su et al. 2014; Chang et al. 2015; Fong et al. 2015; Jensen et al. 2015; Pan et al. 2015; Wang et al. 2016), birth measures (Zhang et al. 2009; Philippat et al. 2012; de Cock et al. 2014; Zhao et al. 2014; Lenters et al. 2015b; Xie et al. 2015; Zhao et al. 2015; Casas et al. 2016), or semen parameters (Zhang et al. 2006; Pant et al. 2008; Jurewicz et al. 2013; Huang et al. 2014; Pant et al. 2014; Specht et al. 2014; Axelsson et al. 2015a; Axelsson et al. 2015b; Lenters et al. 2015a; Pan et al. 2015; Wang et al. 2015b; Thurston et al. 2016). There was inadequate evidence or no evidence of association between the remaining phthalates and the outcomes (Table 9-46). More detail is provided in Health Canada (2016a).

Table 9-46. Summary of levels of evidence of associations between additional phthalates and health outcomes

Outcome	BBP (MBP, MBzP)	DBP (MBP, etc.)	DEHP (MEHP, MEOHP, MEHHP, MECPP, MCMHP)	DnHP (MnHP)	DIOP
Sex hormone levels	IA (9)	NA (1)	LA (17)	NM	NM
Anogenital distance	NA (3)	NM	IA (4)	NM	NM
Birth measures	IA (4)	IA (2)	LA (11)	NM	NM
Male infant genitalia	NA (1)	NM	NA (2)	NM	NM
Preterm birth and gestational age	IA (4)	NM	IA (5)	NM	NM
Altered male puberty	NA (2)	NM	IA (4)	NM	NM
Gynecomastia	NA (1)	NM	NA (2)	NM	NM
Changes in semen	IA (8)	NA (1)	LA (11)	NM	NM

parameteres					
Pregnancy loss	NA (3)	NM	IA (4)	NM	NM
Altered time to pregnancy	IA (2)	NA (1)	NA (2)	NM	NM

() = Number of studies.

NM = Not measured in studies of quartile 2 and above (See Health Canada [2016a] for more details).

NA = No evidence of association.

IA = Inadequate evidence of an association.

LA = Limited evidence of an association.

MBP = Monobutyl phthalate.

MBzP = Monobenzyl phthalate.

MCMHP = Mono[2-(carboxymethyl)hexyl] phthalate.

MEHP = Mono(2-ethyl hexyl)phthalate.

MEOHP = Mono(2-ethyl-5-oxohexyl) phthalate.

MEHHP = Mono(2-ethyl-5-hydroxyhexyl) phthalate.

MECPP = Mono(2-ethyl-5-carboxypentyl) phthalate.

MnHP = Mono-h-hexyl phthalate.

9.2.3 Long-chain phthalates

DIDP

The LCP SOS (Environment Canada, Health Canada 2015d) summarizes the health effects literature related to DIDP. No new animal hazard studies were identified after the literature cut-off date of the LCP SOS.

Table 9-47 provides critical endpoints and corresponding NOAEL and/or LOAEL values for DIDP, as previously described in LCP SOS (Environment Canada, Health Canada 2015d).

Table 9-47. Summary of critical systemic effects after oral exposure to DIDP

Endpoint	Species	Effect	LOAEL (mg/kg-bw/day)	NOAEL (mg/kg-bw/day)	Reference
Short term	Rat	Increase in liver weight in males accompanied with histological changes at the highest dose	300	300 (females)	BIBRA 1986
Subchronic	Dog	Increase in liver weight accompanied with histological changes.	75	15	Hazleton Laboratories 1968b
Chronic	Rat	Histopathological changes in the liver in males.	22	N/A	Cho et al. 2008

N/A = Not applicable

DUP

The LCP SOS (Environment Canada, Health Canada 2015d) summarizes the health effects literature related to DUP. No new literature was identified after the literature cut-off date of the LCP SOS. Table 9-48 provides critical endpoints and corresponding NOAEL and/or LOAEL values for DUP, as previously described in LCP SOS (Environment Canada, Health Canada 2015d).

Table 9-48. Summary of critical systemic effects associated with oral exposure to DUP

Endpoint	Species	Effect	LOAEL (mg/kg-bw/day)	NOAEL (mg/kg-bw/day)	Reference
Short term	Rat	Decreased body weight gain and increased liver and kidney weights accompanied with liver lesions	1145	282	Barber et al. 1987
Subchronic	Rat (DnOP)	Increases in liver enzyme activities and histological effects in the liver and thyroid	≤ 350-403	37	Poon et al. 1997

Evidence in humans

A literature update was also conducted to identify any recent human data for long-chain phthalates. The search was focused on reproductive and developmental endpoints in males as these endpoints were identified as critical health endpoints in the SOS reports. No information is currently available on the potential reproductive-developmental effects of DUP in humans. Studies identified for DIDP were further evaluated and scored for quality using a consistent evaluation metric (Downs and Black 1998).

For the health outcomes evaluated (i.e., sex hormone levels, anogenital distance, birth measures, male infant genitalia, preterm birth and gestational age, altered male puberty, gynecomastia, changes in semen parameters, pregnancy loss, and altered time to pregnancy), there was no evidence of association between any of the long-chain phthalates evaluated and the outcomes (Table 9-49). More detail is provided in Health Canada (2016a).

Table 9-49. Summary of levels of evidence of associations between long-chain phthalates and health outcomes

Outcome	DIDP (MIDP/MCINP)
Sex hormone levels	NA (1)
Anogenital distance	NA (1)
Birth measures	NA (1)

Male infant genitalia	NM
Preterm birth and gestational age	NA (1)
Altered male puberty	NM
Gynecomastia	NM
Changes in semen parameteres	NM
Pregnancy loss	NA (1)
Altered time to pregnancy	NM

() = Number of studies.

NM = Not measured in studies of quartile 2 and above (See Health Canada [2016a] for more details).

NA = No evidence of association.

IA = Inadequate evidence of an association.

LA = Limited evidence of an association.

MIDP = Monoisodecyl phthalate.

MCINP = Mono(carboxyisononyl) phthalate.

9.3 Characterization of risk to human health

9.3.1 Short-chain phthalates

DMP

Table 9-50 provides all relevant exposure and hazard values for DMP, as well as resultant margins of exposure (MOEs), for determination of risk, which were previously described in the SCP SOS (Environment Canada, Health Canada 2015a). Overall, the MOEs for DMP are considered to be adequate to account for uncertainties in the exposure and health effect databases.

Table 9-50. Summary of MOEs to DMP for subpopulations with highest exposure

Age group and exposure scenario	Central tendency (upper bounding) estimate of exposure (µg/kg bw/day)	Level and basis for NOAEL (mg/kg-bw/day)	MOE^d
Children (males) 2–3 years: biomonitoring, MIREC CD Plus	0.19 (0.66)	NOAEL = 230 (chronic dermal, DEP) Decrease in absolute brain weight in males (NTP 1995)	> 1 million (340 000)
Infants 0–6 months, breast milk fed: environmental media and food, oral and inhalation	0.019 (0.26)	LOAEL = 1862 (pubertal, 7 days oral, DMP) ↓ serum and testicular testosterone, dihydrotestosterone concentrations and ↑ absolute, relative liver weight (Oishi and Hiraga 1980) (no NOAEL)	> 1 million
Infants 0–6 months: diaper cream, dermal	2.7 ^a (8.2) ^a	NOAEL = 200 (subchronic dermal, DMP) Changes in nervous system and renal function in males (Timofieyskaya 1976)	74 000 (24 000)
Adults (females) 20+ years: biomonitoring, NHANES	0.027 (0.26)	NOAEL = 415 (chronic dermal, DEP) Decrease in BW of 8% in females (NTP 1995)	> 1 million
Adolescents (males) 12–19 years: biomonitoring, NHANES	0.042 (0.29)	NOAEL = 230 (chronic dermal, DEP) Decrease in absolute brain weight in males (NTP 1995)	> 1 million (790 000)
Adolescents 12–19 years: environmental media and food, oral and inhalation	0.0085 (0.091)	NOAEL = 750 (in utero oral DMP) Highest dose tested for potential RPS effects (Gray et al. 2000; Furr et al. 2014)	> 1 million ^b
Adults 20+ years: hairspray, dermal	66 ^{ac} (200) ^a	NOEL = 230 (chronic dermal, DEP) Decrease in absolute brain weight in males (NTP 1995)	3500 (1150)

<p>Adults 20+ years: hair dye, dermal</p>	<p>1400^{ac} (4200)^a</p>	<p>NOAEL = 2380 (short term dermal, DMP) slight ↓body weight in dams (Hansen and Meyer 1989)</p>	<p>1700 (570)</p>
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^a External dermal exposure estimates

^b This margin is also protective for potential effects of DMP (based on effects observed with DEP) on males of this age group which occur at higher doses.

^c Lower-bound estimate: based on minimum concentration

^d Margin of exposure: central tendency and (upper bounding)

9.3.2 Medium-chain phthalates, additional phthalates and cumulative risk assessment

The critical effects of concern of medium-chain phthalates consisted of adverse effects on the development of the male reproductive system following gestational exposure, with a particular focus on RPS-related parameters that were identified in the rat, the most sensitive species. These parameters are considered adverse and relevant for characterizing risk of exposure of the general Canadian population to this subgrouping of phthalates. Please see MCP SOS (Environment Canada, Health Canada 2015b) for a general summary and rationale.

In cases where limited rat studies were available, effect levels in other species (i.e., mice) that were lower than in rats were used for risk characterization. Evidence in humans, based on the Downs and Black scoring system (Downs and Black 1998), indicated limited evidence of association between DINP and sex hormone levels or semen parameters and between DEHP and sex hormone levels, birth measures or semen parameters. This supports the selection of the mode of action for risk characterization.

In the following sections, human health risk from exposure to medium-chain phthalates within the Phthalate Grouping is characterized on an individual basis, followed by a cumulative risk assessment to address the potential risk of concurrent exposure to medium-chain phthalates exhibiting a similar mode of action.

9.3.2.1 Individual risk characterization of the original medium-chain subgroup

DIBP

Table 9-51 provides all relevant exposure and hazard values for DIBP, as well as resultant MOEs, for determination of risk, which were previously described in the MCP SOS (Environment Canada, Health Canada 2015b). Overall, the MOEs for DIBP are considered to be adequate to account for uncertainties in the exposure and health effect databases. From the information available, there is evidence that DIBP elicits effects on the developing male reproductive system, indicative of RPS, which suggests that DIBP has a common mode of action with other phthalates in this grouping.

Table 9-51. Summary of MOEs to DIBP for relevant subpopulations with highest exposure

Age group and exposure scenario	Central tendency (upper bounding) estimate of exposure (µg/kg bw/day)	Level and basis for oral NOAEL (mg/kg-bw/day)	MOE^c
Children (males and females) 6–11 years: biomonitoring, CHMS	1.5 (5.3)	NOAEL = 300 Testicular pathology at 500 mg/kg-bw/day (7 d) (Zhu et al. 2010)	200 000 (60 000)
Infants 0–6 months (breastfed): environmental media and food	1.6 (5.9)	NOAEL = 300 Testicular pathology at 500 mg/kg-bw/day (7 d) (Zhu et al. 2010)	200 000 (50 000)
Infants/children (0–18 months)^a: contact plastic articles, dermal	30.7 ^b (245.3)	NOAEL = 300 Testicular pathology at 500 mg/kg-bw/day (7 d) (Zhu et al. 2010)	10 000 (1200)
Infants (0–18 months): mouthing toys, oral	62.8 ^b (251.0)	NOAEL = 300 Testicular pathology at 500 mg/kg-bw/day (7 d) (Zhu et al. 2010)	5000 (1200)
Adults (females) 20–49 years: biomonitoring, CHMS	0.56 (1.4)	NOAEL = 125 Reduced AGD, NR, effects on fertility and other TDS effects at the next highest dose (250 mg/kg-bw/day) (Saillenfait et al. 2008; Furr et al. 2014)	220 000 (89 000)
Adults 20–59 years^a: chronic body lotion, dermal	0.030	NOAEL = 125 Reduced AGD, NR, effects on fertility and other TDS effects at the next highest dose (250 mg/kg-bw/day) (Saillenfait et al. 2008; Furr et al. 2014)	> 1 million

<p>Adults (20+): contact plastic articles, dermal</p>	<p>30.8^b (96.3)</p>	<p>NOAEL = 125 Reduced AGD, NR, effects on fertility and other TDS effects at the next highest dose (250 mg/kg-bw/day) (Saillenfait et al. 2008; Furr et al. 2014)</p>	<p>4060 (1300)</p>
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^a Estimate adjusted on the basis of 10% dermal absorption of DBP.

^b Estimated lower-end exposure.

^c Margin of exposure: central tendency and (upper bounding)

TDS = human testicular dysgenesis syndrome

DCHP

Table 9-52 provides all relevant exposure and hazard values for DCHP, as well as resultant MOEs, for determination of risk, which were previously described in the MCP SOS (Environment Canada, Health Canada 2015b). Overall, the MOEs for DCHP are considered to be adequate to account for uncertainties in the exposure and health effect databases. From the information available, there is evidence that DCHP has effects on the developing male reproductive system, indicative of RPS, which suggests that DCHP has a common mode of action with other phthalates in the grouping.

Table 9-52. Summary of MOEs to DCHP for relevant subpopulations with highest exposure

<p>Age group and exposure scenario</p>	<p>Central tendency (upper bounding) estimate of exposure (µg/kg bw/day)</p>	<p>Level and basis for oral NOAEL (mg/kg-bw/day)</p>	<p>MOE^b</p>
<p>Children 6 months to 4 years: indoor air and dust, dermal and inhalation</p>	<p>0.0018 (0.15)</p>	<p>NOAEL = 25 Increased relative liver weight (females), accompanied by histological changes in the liver and kidneys in both sexes at the two highest doses tested (subchronic) (de Ryke and Willems 1977)</p>	<p>> 1 million (170 000)</p>
<p>Adolescents 12–19^a years: indoor air and dust, dermal and inhalation</p>	<p>< 0.001 (0.065)</p>	<p>LOAEL = 10-20 Testicular pathological changes after in utero exposure during GD12-21 (Li et al. 2016). Reduced AGD, testicular</p>	<p>> 1 million (155 000–310 000)</p>

		<p>pathology and increased resorption after in utero exposure during GD6-19 (Ahabab and Barlas 2015). Antiandrogenic effects (decreased AGD and retained nipples, decreased testosterone production) in F1 and F2 males at higher dose levels in a two-generation study in rats (Hoshino et al. 2005)</p>	
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^a MOEs were calculated for non-pregnant individuals (male and female) and pregnant females for this age group.

^b Margin of exposure: central tendency and (upper bounding)

DMCHP

Table 9-53 provides all relevant exposure and hazard values for DMCHP, as well as resultant MOEs, for determination of risk, which were previously described in the MCP SOS (Environment Canada, Health Canada 2015b). Overall, the MOEs for DMCHP are considered to be adequate to account for uncertainties in the exposure and health effect databases. From the information available, there is evidence that DMCHP has effects on the developing male reproductive system, indicative of RPS, which suggests that DMCHP has a common mode of action with other phthalates in the grouping.

Table 9-53. Summary of MOEs to DMCHP for relevant subpopulations with highest exposure

Age group and exposure scenario	Central tendency (upper bounding) estimate of exposure (µg/kg bw/day)	Level and basis for oral NOAEL (mg/kg-bw/day)	MOE ^b
Infants 0–6 months: dust ingestion, oral	0.0027 (0.054)	NOAEL _{DCHP} = 25 Increased relative liver weight (females), accompanied by histological changes in the liver and kidneys in both sexes at the two highest doses tested (subchronic) (de Ryke and Willems 1977)	> 1 million (460 000)
Adolescents 12–19^a years: dust ingestion, oral	< 0.001	LOAEL _{DCHP} = 10-20 Testicular pathological changes after in utero exposure during	> 1 million

		<p>GD12-21 (Li et al. 2016). Reduced AGD, testicular pathology and increased resorption after in utero exposure during GD6-19 (Ahabab and Barlas 2015). Antiandrogenic effects (decreased AGD and retained nipples, decreased testosterone production) in F1 and F2 males at higher dose levels in a two-generation study in rats (Hoshino et al. 2005)</p>	
<p>Adults 20+^a years: dust ingestion, oral</p>	<p>< 0.001</p>	<p>LOAEL_{DCHP} = 10-20</p> <p>Testicular pathological changes after in utero exposure during GD12-21 (Li et al. 2016). Reduced AGD, testicular pathology and increased resorption after in utero exposure during GD6-19 (Ahabab and Barlas 2015). Antiandrogenic effects (decreased AGD and retained nipples, decreased testosterone production) in F1 and F2 males at higher dose levels in a two-generation study in rats (Hoshino et al. 2005)</p>	<p>> 1 million</p>

^a MOEs were calculated for non-pregnant individuals (male and female) and pregnant females for this age group.

^b Margin of exposure: central tendency and (upper bounding)

DBzP

Table 9-54 provides all relevant exposure and hazard values for DBzP, as well as resultant MOEs, for determination of risk, which were previously described in the MCP SOS (Environment Canada, Health Canada 2015b). Overall, the MOEs for DBzP are considered to be adequate to account for uncertainties in the exposure and health effect databases. From the information available, there is evidence that DBzP has effects on the developing male reproductive system, indicative of RPS, which suggests that DBzP has a common mode of action with other phthalates in the grouping.

Table 9-54. Summary of MOEs to DBzP for relevant subpopulations with highest exposure

Age group and exposure scenario	Central tendency (upper bounding) estimate of exposure (µg/kg bw/day)	Level and basis for oral NOAEL (mg/kg-bw/day)	MOE ^b
Infants 0–6 months: dust ingestion, oral	0.016 (0.097)	LOAEL _{MBzP} = 167 decrease in body weight gain and food consumption (Ema et al. 2003)	> 1 million
Adolescents 12–19^a years: dust ingestion, oral	< 0.001 (0.0011)	NOAEL _{MBzP} = 167 anti-androgenic effects in utero LOAEL _{MBzP} = 167 decrease in body weight gain and food consumption (Ema et al. 2003)	> 1 million

^a MOEs were calculated for non-pregnant individuals (male and female) and pregnant females for this age group.

^b Margin of exposure: central tendency and (upper bounding)

B84P

Table 9-55 provides all relevant exposure and hazard values for B84P, as well as resultant MOEs, for determination of risk, which were previously described in the MCP SOS (Environment Canada, Health Canada 2015b). Overall, the MOEs for B84P are considered to be adequate to account for uncertainties in the exposure and health effect databases. From the information available, there is evidence that B84P has effects on the developing male reproductive system, indicative of RPS, which suggests that B84P has a common mode of action with other phthalates in the grouping.

Table 9-55. Summary of MOEs to B84P for relevant subpopulations with highest exposure

Age group and exposure scenario	Central tendency (upper bounding) estimate of exposure (µg/kg bw/day)	Levels and basis for oral NOAEL (mg/kg-bw/day)	MOE^d
Infants (0–18 months): exposure to plastic articles, dermal	2.7 ^c (21.6)	NOAEL (BBP)= 151 ^b Histopathological changes in the pancreas, gross pathological alterations in the liver and significant increase in relative kidney weight in male rats at next highest dose of 381 mg/kg-bw/day (subchronic) (NTP 1997)	56 000 (6990)
Infants 0–6 months: dust ingestion, oral	0.0063 (0.047)	NOAEL (BBP)= 151 ^b Histopathological changes in the pancreas, gross pathological alterations in the liver and significant increase in relative kidney weight in male rats at next highest dose of 381 mg/kg-bw/day (subchronic) (NTP 1997)	> 1 million
Adults (20+): exposure to plastic articles, dermal	2.7 ^c (8.5)	NOAEL (BBP) = 50 Decreased pup body weight (male and female) and ↓AGD at birth in F2 males at next highest dose of 100 mg/kg-bw/day; decreased fetal testosterone (Aso et al. 2005; Nagao et al. 2000; Tyl et al. 2004; Furr et al. 2014)	19 000 (5900)

^a MOEs were calculated for non-pregnant individuals (male and female) and pregnant females for these age groups.

^b NOAEL (BBP prepubertal) = 300 (testicular pathology at 500 mg/kg-bw/day [7d]) is at higher doses than the systemic effects.

^c Estimated lower-end exposure, adjusted for dermal absorption (10%).

^d Margin of exposure: central tendency and (upper bounding)

DIHepP

Table 9-56 provides all relevant exposure and hazard values for DIHepP, as well as resultant MOEs, for determination of risk, which were previously described in the MCP SOS (Environment Canada, Health Canada 2015b). Overall, the MOEs for DIHepP are

considered to be adequate to account for uncertainties in the exposure and health effect databases. From the information available, there is evidence that DIHepP has effects on the developing male reproductive system, indicative of RPS, which suggests that DIHepP has a common mode of action with other phthalates in the grouping.

Table 9-56. Summary of MOEs to DIHepP for relevant subpopulations with highest exposure

Age group and exposure scenario	Central tendency (upper bounding) estimate of exposure (µg/kg bw/day)	Level and basis for oral NOAEL (mg/kg-bw/day)	MOE ^b
Infants 0–6 months: dust ingestion, oral	0.096 (1.1)	NOAEL = 50-162 Increased liver and kidney weights with histopathological findings at 222–716 mg/kg-bw/day (McKee et al. 2006)	520 000– > 1 million (45 000– 150 000)
Adolescents 12–19^a years: dust ingestion, oral	0.0011 (0.013)	NOAEL = 50–168 Significant reduction in AGD and body weight in male F2 pups after in utero exposure to DIHepP at the next highest dose tested in rats (309–750 mg/kg-bw/day) and liver and kidney effects at the next highest dose (227–750 mg/kg-bw/day) in F1 rats (McKee et al. 2006)	> 1 million

^a MOEs were calculated for non-pregnant individuals (male and female) and pregnant females for this age group.

^b Margin of exposure: central tendency and (upper bounding)

B79P

Table 9-57 provides all relevant exposure and hazard values for B79P, as well as resultant MOEs, for determination of risk. Overall, the MOEs for B79P are considered to be adequate to account for uncertainties in the exposure and health effect databases. From the information available, there is evidence that B79P has effects on the developing male reproductive system, indicative of RPS, which suggests that B79P has a common mode of action with other phthalates in the grouping.

Table 9-57. Summary of MOEs to B79P for relevant subpopulations with highest exposure

Age group and exposure scenario	Central tendency (upper bounding) estimate of exposure (µg/kg bw/day)	MOE ^b based on an oral NOAEL _{DINP} of 15 mg/kg-bw/day from Lington et al. 1997
Infants (0–18 months): exposure to plastic articles, dermal	2.7 ^a (21.6)	5600 (690)
Adults (20+): contact with plastic articles, dermal	2.7 ^a (8.5)	5600 (1800)
Infants 0–6 months: dust ingestion, oral	0.0063 (0.047)	> 1 million (319 149)
Adolescents 12–19 ^a years: dust ingestion, oral	< 0.001	> 1 million

^a Estimated lower-end exposure.

^b Margin of exposure: central tendency and (upper bounding)

DINP

Table 9-58 provides all relevant exposure and hazard values for DINP, as well as resultant MOEs, for determination of risk. Overall, the MOEs for DINP are considered to be adequate to account for uncertainties in the exposure and health effect databases. From the information available, there is evidence that DINP has effects on the developing male reproductive system, indicative of RPS, which suggests that DINP has a common mode of action with other phthalates in the grouping.

Table 9-58. Summary of MOEs to DINP for subpopulations with highest exposure

Age group and exposure scenario	Central tendency (upper bounding) estimate of exposure (µg/kg bw/day)	Level and basis for oral NOAEL (mg/kg-bw/day)	MOE ^d
Children (females) 6–11 years: biomonitoring, 95th percentile, NHANES ^b	3.8 (26)	NOAEL = 15 Increase in liver and kidney weights,	4000 (580)

Age group and exposure scenario	Central tendency (upper bounding) estimate of exposure (µg/kg bw/day)	Level and basis for oral NOAEL (mg/kg-bw/day)	MOE ^d
		increased peroxisomal enzyme levels and histological changes in both organs at 152-184 (Lington et al. 1997)	
Infants/children 6 months to 4 years: food and dust, oral	1.8 (19.7)	NOAEL = 15 Increase in liver and kidney weights, increased peroxisomal enzyme levels and histological changes in both organs at 152-184 (Lington et al. 1997)	8300 (760)
Infants (0 to 18 months): mouthing plastic toys and articles, oral	30 ^c (120)	NOAEL = 15 Increase in liver and kidney weights, increased peroxisomal enzyme levels and histological changes in both organs at 152-184 (Lington et al. 1997)	500 (125) ^e
Infants (0 to 18 months): exposure to plastic articles, dermal	1.1 ^c (8.6)	NOAEL = 15 Increase in liver and kidney weights, increased peroxisomal enzyme levels and histological changes in both organs at 152-184 (Lington et	14 000 (1700)

Age group and exposure scenario	Central tendency (upper bounding) estimate of exposure (µg/kg bw/day)	Level and basis for oral NOAEL (mg/kg-bw/day)	MOE ^d
<p>Adults (females) 20+ years: biomonitoring: 95th percentile, NHANES^b</p>	<p>2.3 (23)</p>	<p>al. 1997) LOEL/NOAEL = 10–15 ↑ MNGs, ↑ Leydig cell clusters/aggregation starting from 100 mg/kg-bw/day after in utero exposure in GD12-21 (Li et al. 2015b), increase in liver and kidney weights, increased peroxisomal enzyme levels and histological changes in both organs at 152–184 (Lington et al. 1997)</p>	<p>4300 to 6500 (430 to 650)</p>
<p>Adults (males) 20+^a years: biomonitoring, 95th percentile, NHANES^b</p>	<p>2.8 (24)</p>	<p>NOAEL = 15 Increase in liver and kidney weights, increased peroxisomal enzyme levels and histological changes in both organs at 152–184 (Lington et al. 1997)</p>	<p>5400 (630)</p>
<p>Adolescents 12 to 19 years: food and dust, oral</p>	<p>1.0 (11.4)</p>	<p>LOEL/NOAEL = 10–15 ↑ MNGs, ↑ Leydig cell clusters/aggregation starting from 100 mg/kg-bw/day after</p>	<p>10 000–15 000 (880–1300)</p>

Age group and exposure scenario	Central tendency (upper bounding) estimate of exposure (µg/kg bw/day)	Level and basis for oral NOAEL (mg/kg-bw/day)	MOE^d
		in utero exposure in GD12-21 (Li et al. 2015b), increase in liver and kidney weights, increased peroxisomal enzyme levels and histological changes in both organs at 152–184 (Lington et al. 1997)	
Adults (females) 20+^a years: exposure to plastic articles, dermal	1.1 ^c (3.4)	LOEL/NOAEL = 10–15 ↑ MNGs, ↑ Leydig cell clusters/aggregation starting from 100 mg/kg-bw/day after in utero exposure in GD12-21 (Li et al. 2015b), increase in liver and kidney weights, increased peroxisomal enzyme levels and histological changes in both organs at 152–184 (Lington et al. 1997)	9100–14 000 (2900–4400)

^a MOEs were calculated for non-pregnant individuals (male and female) and pregnant females for this age group.

^b The highest intakes at the 95th percentile (33 µg/kg bw/day: 12-to-19-year-old males and 27 ug/kg/day: 12-to-19-year old females) were not brought forward to risk characterization because the relative standard error of the data was greater than 30%. For children aged 6 to 11 years, 26 µg/kg bw/d (RSE > 30%) was carried forward to risk characterization in order to be protective of this age group and because of the absence of low variability data, at the upper percentiles, for another comparable age group. For more details, see Environment Canada, Health Canada 2015c.

^c Estimated lower end exposure.

^d Margin of exposure: central tendency and (upper bounding)

^e Migration rates used to estimate exposure were based on concentrations in toys (12.9 - 77%) that are higher than concentrations observed in recent Health Canada surveys (see Table 9-3, Environment Canada, Health Canada

2015c). Currently, Canada (like the United States and the European Union) have regulations (0.1%) in place limiting the amount of certain phthalates (including DINP) in toys and childcare articles.

CHIBP, BHP and BIOP

An examination of the potential developmental and reproductive toxicity of CHIBP, BHP and BIOP using appropriate analogues for read-across revealed that these medium-chain phthalates have the potential to have significant effects on the developing male, in addition to systemic effects (liver, kidney).

On the basis of the information available, it can be concluded that CHIBP, BHP and BIOP meet the criteria for inclusion in the evaluation of the potential cumulative risk of phthalates on the developing male reproductive system given the evidence of the effects of their analogues; however, there is no exposure at this time. Consequently, the risk to human health for these substances is not expected.

Although the above MOEs for the medium-chain phthalates in the Phthalate Substance Grouping described in this section are considered adequate on an individual basis, this does not address the potential risk of concurrent exposure to these substances and other phthalates exhibiting a similar mode of action. Hence, all 10 medium-chain phthalates in the Phthalate Substance Grouping will be included for risk characterization in a cumulative context.

9.3.2.2 Cumulative risk assessment

The human health approach for a CRA for this Grouping has been described in detail in the “Proposed approach for cumulative risk assessment of certain phthalates under the Chemicals Management Plan” document (Environment Canada, Health Canada 2015e).

Human health-focused approaches for quantifying the cumulative risk of phthalates have been conducted by several national organizations including the Australian Department of Health (AGDH 2012, 2013, 2014a,b), the Danish Environmental Protection Agency (Danish EPA 2011), and the recently completed assessment by the United States Chronic Health Advisory Panel (US CPSC CHAP 2014). This draft screening assessment uses a tiered approach, following the schematic of the World Health Organization (WHO) and the International Program on Chemical Safety (IPCS) Framework for Risk Assessment of Combined Exposures to Multiple Chemicals (WHO 2009; Meek et al. 2011). This framework exercises the default assumption that the substances being assessed act by dose addition and the evaluation of cumulative risk involves multiple tiers where each higher level is increasingly dependent on additional data. The lower tier begins with simple assumptions and/or surrogate data for both hazard and exposure and refinement to a higher tier occurs if required and as the data allows.

For exposure characterization, if there is sufficient evidence of co-occurrence, then a CRA can be considered. The exposure approach is described in the CRA approach document (Environment Canada, Health Canada 2015e).

In summary, the pivotal information that determined substances for inclusion into the CRA were industry data collected under section 71 of CEPA (Environment Canada 2014), detection in North American biomonitoring surveys (CHMS, MIREC, MIREC-CD Plus, P4, NHANES; Health Canada 2011b; Health Canada 2013; personal communication from EHSRD, Health Canada, to ESRAB, Health Canada, October 2013, 2014, unreferenced; Arbuckle et al. 2014; CDC 2014), and detection in household dust (CHDS; Kubwabo et al. 2013). For phthalate parent compounds (i.e., DEHP, DIBP, DBP, BBP, and DINP), with close to a 100% detection in various biomonitoring surveys, there was sufficient evidence for co-exposure; these substances were therefore assessed for cumulative risk.

A significant number of phthalates within the medium-chain phthalates subgroup have not been monitored in biomonitoring samples, but are found in commerce in Canada. These substances (i.e., DIHepP, B79P, B84P, DCHP, and DIOP) were included in the assessment of cumulative risk on the basis of their in-commerce status coupled with close to 100% detection in dust samples from Canadian homes.

Finally, given reporting limits and difficulties in determining import activity of substances, the CEPA section 71 survey may not have captured all in-commerce activity. As a result, substances that fit the profile of non-reporting to section 71 and close to 100% detection in house dust samples were also assessed for cumulative risk (i.e., DMCHP, DBzP, and DnHP).

There were three populations of interest for which exposure estimates were considered for cumulative risk: pregnant women and women of childbearing age (characterized as women aged twelve and up), infants (covered by age groups 0 to 6 months, 6 months to 4 years and 3 to 5 years¹⁵), and children (covered by age groups 6 months to 4 years and 5 to 11 years). Adolescents and adult males were covered by this approach as they had generally lower estimates of phthalate exposure and are considered less sensitive to the reproductive effects of medium-chain phthalates compared to younger males (i.e. children) (NAS 2008).

In terms of exposure estimates considered for cumulative risk, biomonitoring data, which generally captures all potential exposure sources and routes (environmental media, food and products available to consumers) was considered a primary source

¹⁵ In all cases, 3- to 5-year exposure intakes (quantified by biomonitoring concentrations) were used as surrogates for infant exposure and risk as this age group showed consistently higher intakes than the infant age group. This is a conservative approach. 0.5- to 4-year exposure intakes (quantified by environmental media and food concentrations) were used to quantify exposure and risk for infants when this group showed higher intakes than for the < 0.5-year-olds.

and estimated monitoring data (chronic exposures resulting from environmental media and food) was considered as a supporting source of information. The US CPSC CHAP (2014) also used biomonitoring data as the primary source of exposure in their CRA. Regardless of route of exposure, phthalates, in general, are not considered acute toxicants, with LD₅₀ levels from dermal exposure being at minimum two- to five-fold higher than oral values, which in turn are also high (Draize et al. 1948; David et al. 2001; Monsanto Company 1970 cited in US EPA 2006, 2010). Since phthalates metabolize relatively quickly showing no accumulation, and excretion is rapid, within hours to days (Phokha et al. 2002; Clewell et al. 2009), acute exposures were not considered relevant for a CRA. It should also be noted that no other jurisdictions have addressed phthalate exposures and risk from acute, one-time, exposures (AGDH 2011; ECHA 2013b; US CPSC CHAP 2014).

Upper-bound exposure estimates were used to estimate individual phthalate levels in the CRA to account for the uncertainties associated with the exposure data. The upper-bound exposure estimates used to estimate cumulative risk for relevant populations for the 16 medium-chain phthalates are summarized in Appendix F (Tables F-1, F-2, F-3 and F-4).

On the basis of the available information on the common adverse effects (RPS) and the observed differences in potencies within the medium-chain phthalates, a lower-tiered hazard characterization using the hazard index (HI) was considered to be the most appropriate approach. The HI method was selected because it offers the benefit of being simple and flexible and allows for an indication of which substance or substances in the CRA, or which source and route, may be the predominant contributor(s) to the overall risk. Identification of the substances or sources and routes that are drivers of the CRA is beneficial for informing risk management.

An HI is the summation of the individual hazard quotients (HQs) for each individual substance to determine the overall cumulative risk of the substance group of interest. The HQ of each substance is the ratio of exposure to a reference value (RfV) which is calculated by dividing the critical effect level identified in the hazard database by a defined uncertainty factor [UF]). The HI equation is as follows: $HI = \sum HQ = \sum (exposure/RfV)$. HI values of the medium-chain phthalates are calculated for the three subpopulations that represented the highest exposure groups.

Critical effect levels have been established at three life stages (i.e., in utero, prepubertal/pubertal, and adult) because of different sensitivity to the adverse effects of phthalates on development and reproduction at different life stages. The critical effect levels identified for the in utero life stage were used to calculate the HI value for pregnant woman and for infants. The critical effect levels identified for the prepubertal/pubertal life stage were used to calculate the HI value for children. The critical effect levels of the in utero and prepubertal/pubertal life stages for the medium-chain phthalates as well as the calculated RfVs are summarized in Appendix F (Table F-5 and F-6).

Given the fact that medium-chain phthalates have similar physical-chemical properties, have similar toxicological effects, and show an overall similarity in strength of their health effect databases (especially in regards to in utero exposure), the same default UF for the two corresponding subpopulations was used to calculate HQ values for each phthalate. A similar approach was adopted by another jurisdiction (US CPSC CHAP 2014). For the calculation of the total HI for pregnant women/women of childbearing age and infants, an UF of 100 (10 for intraspecies and 10 for interspecies differences) was used to calculate the RfV for the critical effect levels identified at the in utero life stage. For children, a default UF of 300 was used to calculate the RfV for the critical effects levels identified for the prepubertal-pubertal life stage. An additional UF of 3 was applied in this case on the basis of the limitations of the health effects database for the prepubertal life stage (quality and quantity of the studies currently available), and taking into consideration the variability in exposure duration in the different studies as well as the possibility that animals might also have been exposed to medium-chain phthalates in utero. The HI values for pregnant women/women of childbearing age, infants, and children are presented in Table 9-59 (also see Appendix F; tables F-7, F-8 and F-9).

Table 9-59. Hazard index values for subpopulations with the highest exposure

Population of interest	Calculated HI with exposure estimates based on biomonitoring (upper bound)	Calculated HI with exposure estimates based on environmental media and food (upper bound)
HI for pregnant women and women of childbearing age	0.24	0.23
HI for infants	0.37	0.82
HI for children	0.54	0.61

Individual phthalates that had the highest contribution to the cumulative risk were identified. Tables F-7, F-8 and F-9 (in Appendix F) show that the same three phthalate compounds (DINP, DBP, DEHP) resulted in the majority of cumulative risk, regardless of the age group or source of exposure data (biomonitoring or environmental media and food). Biomonitoring exposure estimates were generally considered more representative of potential exposures, including products available to consumers (regardless of source, route or duration). As a result, the HI values calculated using biomonitoring were considered more realistic but still conservative, because they were calculated using upper-bound exposure estimates.

Children and infants had higher HI values compared to pregnant women and women of childbearing age (aged 12 years and over). HI values calculated using biomonitoring data were lower than those calculated using environmental and dietary monitoring data for infants and children. In the case of DEHP, the high exposures from food were expected to be as a result of the unexpected presence of DEHP in fruits and vegetables which would have overestimated actual dietary exposure to DEHP. Nonetheless, this conservative, lower-tiered HI approach indicated no concern for potential cumulative risk of medium-chain phthalates for the general Canadian population, specifically the

more sensitive subpopulations (pregnant women/women of childbearing age, infants, and children) at current exposure levels.

An HI value greater than 1 would indicate the need for further investigation or refinement. The HI values for the three subpopulations with the highest exposures were all below 1. Therefore, further refinement to a higher-tiered assessment is not necessary at this time. While risk is low at current levels for the cumulative risk of medium-chain phthalates (Phthalate Substance Grouping: DIBP, CHIBP, BChP, DChP, DBzP, B79P, DMChP, DIHepP, BIOP, B84P, DINP; Additional phthalates: DPrP, DBP, BBP, DnHP, 79P, DIOP, DEHP), an increase in exposure levels could represent a potential risk to human health.

9.3.3 Long-chain phthalates

DIDP

Table 9-60 provides all relevant exposure and hazard values for DIDP, as well as resultant MOEs, for determination of risk, which were previously described in the LCP SOS (Environment Canada, Health Canada 2015d). Overall, the MOEs for DIDP are considered to be adequate to account for uncertainties in the exposure and health effect databases.

Table 9-60. Summary of MOEs to DIDP for subpopulations with highest exposure

Age group and exposure scenario	Central tendency (upper bounding) estimate of exposure (µg/kg bw/day)	MOE^c based on an oral LOAEL of 22 mg/kg-bw/day from Cho et al. 2008
Children (males) 6–11 years: biomonitoring, mean (95th percentile), NHANES	1.4 (4.4)	16 000 (5000)
Infants (0–18 months)^a: Exposure to plastic articles, dermal	0.27 ^b (2.16)	81 000 (10 000)
Children 6 months to 4 years: food and dust, oral	0.514 (2.87)	43 000 (7700)
Adolescents 12–19 years: food and dust, oral	0.075 (0.726)	290 000 (30 000)
Adults (males) 20+ years: biomonitoring, mean (95th percentile), NHANES	0.76 (4.4)	29 000 (5000)

Age group and exposure scenario	Central tendency (upper bounding) estimate of exposure (µg/kg bw/day)	MOE ^c based on an oral LOAEL of 22 mg/kg-bw/day from Cho et al. 2008
Adults (females) 20+ years: biomonitoring, mean (95th percentile), NHANES	0.65 (4.9)	34 000 (4500)
Adults 20–59 years: food and dust, oral	0.068 (0.715)	320 000 (31 000)
Adults 20+ ^a years: exposure to plastic articles, dermal	0.27 ^b (0.85)	81 000 (26 000)

^a Estimate adjusted on the basis of 1% dermal absorption of DIDP.

^b Estimated lower end exposure.

^c Margin of exposure: central tendency and (upper bounding)

DUP

Table 9-61 provides all relevant exposure and hazard values for DUP, as well as resultant MOEs, for determination of risk, which were previously described in the LCP SOS (Environment Canada, Health Canada 2015d). Overall, the MOEs for DUP are considered to be adequate to account for uncertainties in the exposure and health effect databases.

Table 9-61. Summary of MOEs to DUP for subpopulations with highest exposure

Age group and exposure scenario	Central tendency (upper bounding) estimate of exposure (µg/kg bw/day)	MOE ^c based on an oral NOAEL of 37 mg/kg-bw/day from Poon et al. 1997 (DnOP)
Infants 0–6 months: dust, oral	0.0198 (0.349)	> 1 million (110 000)
Infants (0–18 months) ^a : exposure to plastic articles, dermal	2.7 ^b (21.6)	14 000 (1700)
Adolescents/Adults 12–19 years: dust, oral	< 0.001 (0.004)	> 1 million
Adults 20+ ^a years: exposure to plastic articles, dermal	2.7 ^b (8.5)	14 000 (4400)

^a Estimate adjusted on the basis of 10% dermal absorption as default.

^b Estimated lower end exposure.

dSAR – Phthalate Substance Grouping

^c Margin of exposure: central tendency and (upper bounding)

9.4 Uncertainties in evaluation of cumulative risk to human health

Uncertainties specific to short-chain, medium-chain, long-chain phthalates and DINP are summarized in the SOS reports (Environment Canada, Health Canada 2015b-e).

The key sources of uncertainty related to the CRA are presented in the table below.

Table 9-62. Sources of uncertainty in the cumulative risk characterization

Key source of uncertainty	Impact
Data availability (multiple species, both sexes, sensitive exposure periods) and data quality for certain phthalates.	+/-
The unknown relevance of the available human epidemiological data studies implicating the potential hazard that certain phthalates pose to humans.	+
The inherent limitations in the use of biomonitoring data for risk characterization related to methods, the chemical-specific variability in levels and metabolites as well as lack of availability of data for certain phthalates.	+/-
The exclusion of estimates of exposure for products available to consumers in the CRA of phthalates, even if biomonitoring estimates would likely capture all exposure sources/routes, including exposure from products available to consumers.	-
The potential toxicokinetic or toxicodynamic differences between species and between the individual chemicals.	+/-
The application of default uncertainty factors for a specific life stage even if some databases are more robust than others as well as the use of life-stage specific studies to determine HIs for children exposed after birth (prepubertal database less robust).	+
The overall cumulative risk of phthalates based on other adverse effects observed after exposure to this grouping as a whole regardless of chain length.	-

+ = uncertainty with potential to cause over-estimation of exposure/risk, - = uncertainty with potential to cause under-estimation of exposure risk, +/- = unknown potential to cause over or under estimation of risk.

Considering the above sources of uncertainty, it is anticipated that the cumulative risk characterization of this grouping would not be sensitive to refinement at this time if additional data were provided, as the lower-tiered HI approach with several conservative assumptions indicated no concern for human health.

10. Conclusion

Considering all available lines of evidence presented in this draft screening assessment, there is low risk of harm to organisms and the broader integrity of the environment from 13 of the phthalates in the Phthalate Substance Grouping (DMP, DIBP, CHIBP, BHP, DCHP, DBzP, DMCHP, DIHP, BIOP, B84P, DINP, DIDP and DUP). However, there is risk of harm to organisms, but not to the broader integrity of the environment, from 1 phthalate included in the Phthalate Substance Grouping, B79P, and 1 additional phthalate, DEHP. DEHP was previously assessed by Environment Canada and Health Canada in 1994 under the Priority Substances Assessment Program. The assessment concluded that DEHP posed a risk to human health in Canada. However, a conclusion for the environment could not be determined because of insufficient information.

It is proposed to conclude that 13 substances in the Phthalate Substance Grouping do not meet the criteria under paragraphs 64(a) or (b) of CEPA as they are not entering the environment in a quantity or concentration or under conditions that have or may have an immediate or long-term harmful effect on the environment or its biological diversity or that constitute or may constitute a danger to the environment on which life depends. It is proposed to conclude that B79P and DEHP meet the criteria under paragraph 64(a) of CEPA as they are entering or may enter the environment in a quantity or concentration or under conditions that have or may have an immediate or long-term harmful effect on the environment or its biological diversity. However, it is proposed to conclude that B79P and DEHP do not meet the criteria under paragraph 64(b) of CEPA as they are not entering the environment in a quantity or concentration or under conditions that constitute or may constitute a danger to the environment on which life depends.

On the basis of the information presented in this draft screening assessment, it is proposed that the 14 phthalates in the Phthalate Substance Grouping do not meet the criteria under paragraph 64(c) of CEPA as they are not entering the environment in a quantity or concentration or under conditions that constitute or may constitute a danger in Canada to human life or health.

Therefore, it is proposed to conclude that B79P and DEHP meet one or more of the criteria set out in section 64 of CEPA. B79P and DEHP have been determined to not meet the persistence and bioaccumulation criteria as set out in the *Persistence and Bioaccumulation Regulations* of CEPA.

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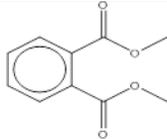
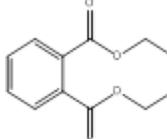
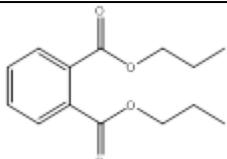
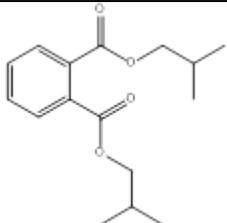
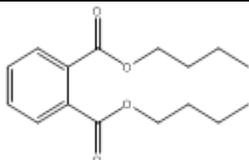
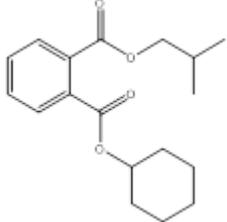
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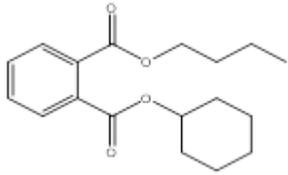
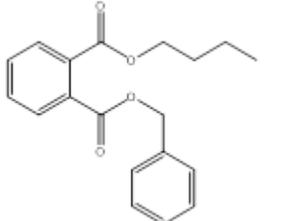
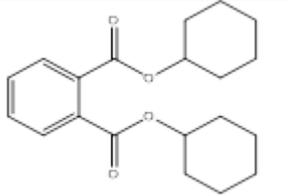
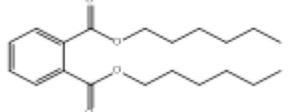
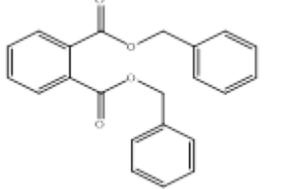
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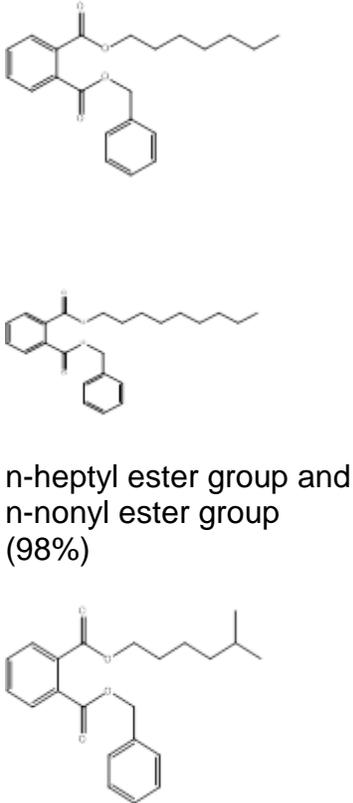
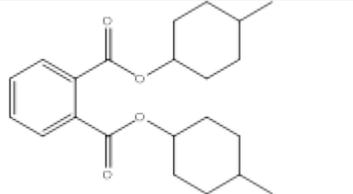
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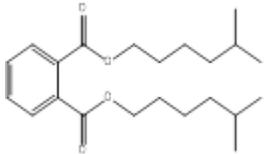
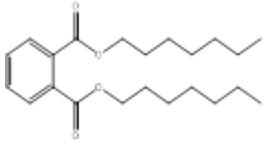
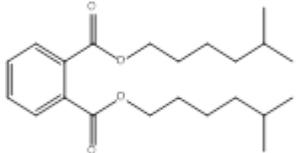
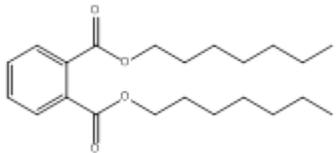
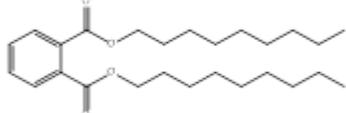
Appendices

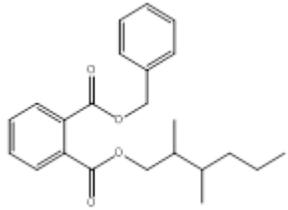
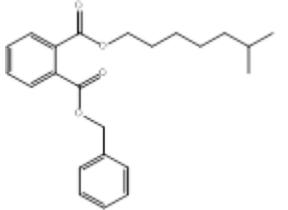
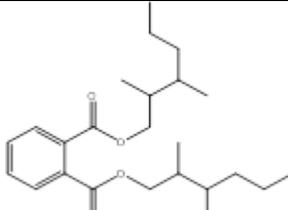
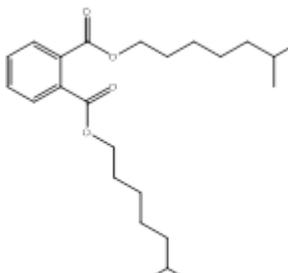
Appendix A. Substance identity and key physico-chemical properties Table A-1.
Substance identity and key physico-chemical properties

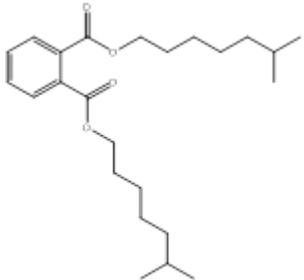
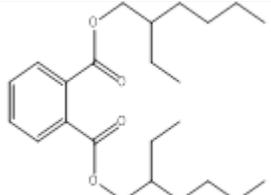
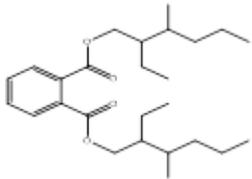
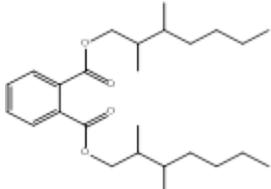
Substance (CAS RN)	Representative structure	Molecular weight (g/mol)	Water solubility (mg/L)	Octanol-water partition coefficient log K_{ow}
DMP (131-11-3)		194.2	4000 (exp) ^a	1.61 (exp) ^h
DEP (84-66-2)		222	930 (Exp) ^a	2.47 (Exp) ^b
DPrP (131-16-8)		250	108 (exp) ^c	3.27 (exp) ^c
DIBP (84-69-5)		278.3	20.3 (exp) ^d	2.91 (EpiSuite 2010; MCI estimate) 3.07 (EpiSuite 2010; log K_{ow} estimate)
DBP (84-74-2)		278.3	11.4 (exp) ^a	4.46 (exp) ^a
CHIBP (5334-09-8)		304.4	6.6 (EpiSuite 2010; WATERNT) 0.323 (EpiSuite 2010; WSKOW) 6.66 (ACD Percepta 2012) 3.04 (VCCLab 2005)	5.33 (EpiSuite 2010) 4.92 (ACD Percepta 2012) 4.28 (VCCLab 2005)

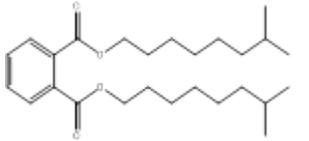
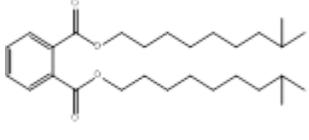
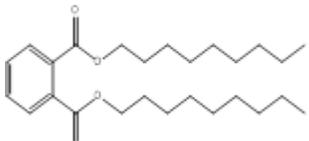
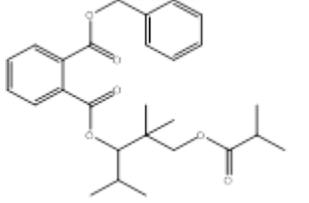
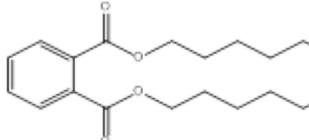
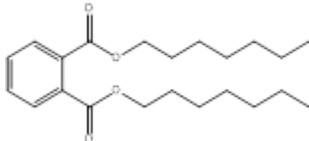
Substance (CAS RN)	Representative structure	Molecular weight (g/mol)	Water solubility (mg/L)	Octanol-water partition coefficient log K_{ow}
BCHP (84-64-0)		304.4	3.94 (EpiSuite 2010; WATERNT) 1.073 (EpiSuite 2010; WSKOW) 4.4 (ACD Percepta 2012) 3.4 (VCCLab 2005)	5.41 (EpiSuite 2010) 5.02 (ACD Percepta 2012) 4.56 (VCCLab 2005)
BBP (85-68-7)		312.3	2.69 (Exp) ^a	4.91 (Exp) ^a
DCHP (84-61-7)		330.4	1.01 (Exp) ^a	4.82 (Exp) ^a
DnHP (84-75-3)		334	3.0×10^{-2} (Exp) ^b	6.82 (Exp) ^b
DBzP (523-31-9)		346.4	0.18 (EpiSuite 2010; WATERNT) 0.30 (EpiSuite 2010; WSKOW) 2.82 (ACD Percepta 2012) 0.72 (VCCLab 2005)	5.08 (EpiSuite 2010) 5.09 (ACD Percepta 2012) 4.63 (VCCLab 2005)

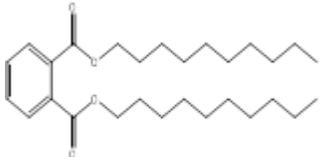
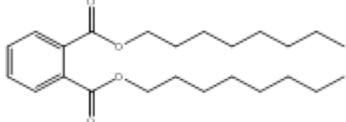
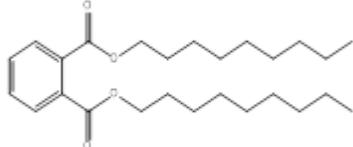
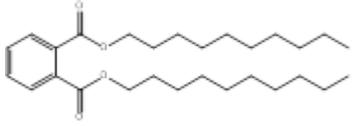
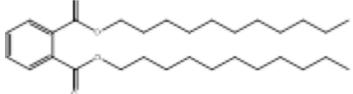
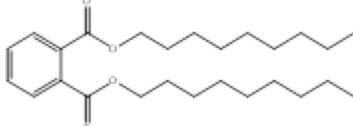
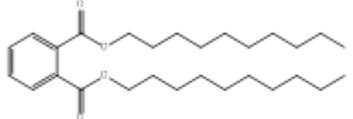
Substance (CAS RN)	Representative structure	Molecular weight (g/mol)	Water solubility (mg/L)	Octanol-water partition coefficient log K_{ow}
B79P (68515-40-2)	 <p data-bbox="407 814 760 919">n-heptyl ester group and n-nonyl ester group (98%)</p> <p data-bbox="407 1203 760 1268">methyl hexyl ester group (2%)</p>	354 – 382	0.3 (Exp) ^a	5.5 (Exp) ^a
DMCHP (27987-25-3)		358.5	0.24 (EpiSuite 2010; WATERNT) 5.38×10^{-3} (EpiSuite 2010; WSKOW) 0.46 (ACD Percepta 2012) 0.31 (VCCLab 2005)	7.04 (EpiSuite 2010) 6.46 (ACD Percepta 2012) 5.47 (VCCLab 2005)

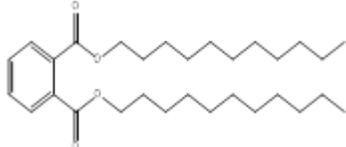
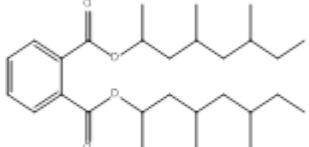
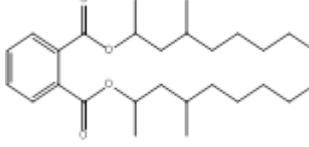
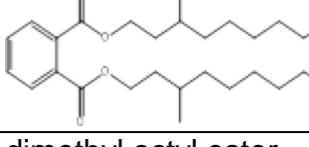
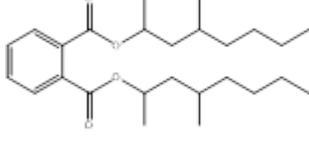
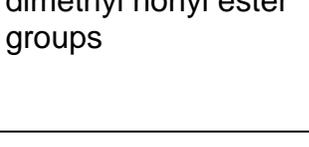
Substance (CAS RN)	Representative structure	Molecular weight (g/mol)	Water solubility (mg/L)	Octanol-water partition coefficient log K_{ow}
DIHepP (71888-89-6)	 <p>methyl hexyl ester groups (mixed isomers) (80%)</p>  <p>n-heptyl ester groups (20%)</p>	362.5	0.017 (exp) ^e	<p>80%: 7.41 (EpiSuite 2010) 6.42 (ACD Percepta 2012) 6.15 (VCCLab 2005)</p> <p>20%: 7.56 (EpiSuite 2010) 7.92 (ACD Percepta 2012) 7.26 (VCCLab 2005)</p>
79P (111381-89-6)	<p>methyl hexyl ester group</p>  <p>n-heptyl ester group</p>  <p>n-nonyl ester group</p> 	362 – 418	<p>1.7×10^{-5} – 2.5×10^{-3} (EpiSuite 2010)</p> <p>0.02 – 0.40 (ACD/Percepta 2012)</p> <p>2.8×10^{-2} – 3.3×10^{-1} (VCCLab 2005)</p>	<p>7.41 – 9.52 (EpiSuite 2010)</p> <p>6.41 – 10.23 (ACD/Percepta 2012)</p> <p>6.15 – 8.46 (VCCLab 2005)</p>

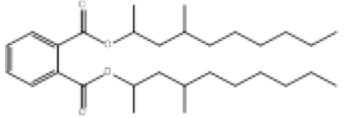
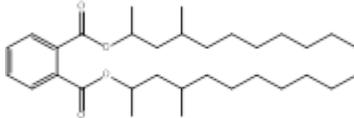
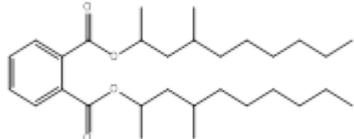
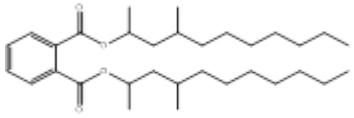
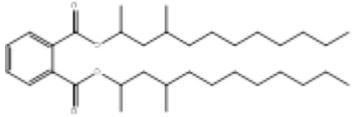
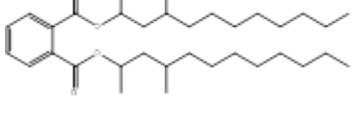
Substance (CAS RN)	Representative structure	Molecular weight (g/mol)	Water solubility (mg/L)	Octanol-water partition coefficient log K_{ow}
BIOP (27215-22-1)	 <p>dimethyl hexyl ester groups (95%)</p>  <p>methyl heptyl ester groups (5%)</p>	368.5	9.8×10^{-3} (EpiSuite 2010; WSKOW) 0.0254 (EpiSuite 2010; WATERNT) 0.423 (VCCLab 2005) 1.50 (ACD Percepta 2012)	6.66 (KOWWIN) 5.87 (VCCLab 2005) 5.81 (ACD Percepta 2012)
DIOP (27554-26-3)	 <p>dimethyl hexyl ester groups (mixed isomers) (75%)</p> 	391	9.0×10^{-2} (Exp) ^b	75%: 8.24 (EpiSuite 2010) 7.52 (ACD Percepta 2012) 6.62 (VCCLab 2005) 25%: 8.39 (EpiSuite 2010) 7.96 (ACD Percepta 2012) 7.02 (VCCLab 2005)

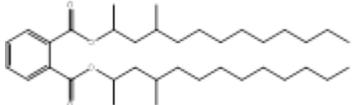
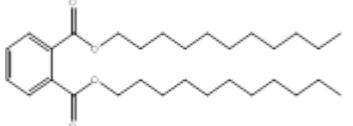
Substance (CAS RN)	Representative structure	Molecular weight (g/mol)	Water solubility (mg/L)	Octanol-water partition coefficient log K_{ow}
	 <p data-bbox="407 636 748 737">methyl heptyl ester groups (mixed isomers) (25%)</p>			
DEHP (117-81-7)		390.6	3.0×10^{-3} (Exp) ^a	7.14 (Exp) ^a
DINP (68515-48-0/ 28553-12-0)	<p data-bbox="407 951 740 1024">methylethyl hexyl ester groups</p>  <p data-bbox="407 1276 708 1350">dimethyl heptyl ester groups</p>  <p data-bbox="407 1623 662 1696">methyl octyl ester groups</p>	419–447	6.0×10^{-4} (Exp) ^a	8.8–9.7 (Exp) ^a

Substance (CAS RN)	Representative structure	Molecular weight (g/mol)	Water solubility (mg/L)	Octanol-water partition coefficient log K_{ow}
	 <p>isodecyl ester groups</p>  <p>n-nonyl ester groups</p> 			
B84P (16883-83-3)		454.6	0.81 (Exp) ^g	7 (Exp) ^a 7.00 (EpiSuite 2010) 6.52 (ACD Percepta 2012) 5.61 (VCCLab 2005)
610P (68648-93-1)	<p>n-hexyl ester groups</p>  <p>n-octyl ester groups</p> 	334–446	3.0×10^{-2} (Exp) ^f	8.17 (Exp) ^f

Substance (CAS RN)	Representative structure	Molecular weight (g/mol)	Water solubility (mg/L)	Octanol-water partition coefficient log K_{ow}
	n-decyl ester groups 			
DnOP (117-84-0)		391	2.2×10^{-2} (Exp) ^a	8.10 (Exp) ^a
D911P (68515-43-5)	n-nonyl ester groups  n-decyl ester groups  n-undecyl ester groups 	418–475	1.6×10^{-7} – 1.7×10^{-5} (EpiSuite 2010) 1.9×10^{-3} – 2.3×10^{-2} (ACD/Percepta 2012) 1.7×10^{-2} – 2.8×10^{-2} (VCCLab 2005)	8.3 (Exp) ^a
D911P-2 (111381-91-0)	n-nonyl ester groups  n-decyl ester groups  n-undecyl ester groups 	418–475	1.6×10^{-7} – 1.7×10^{-5} (WSKOWWIN) 1.9×10^{-3} – 2.3×10^{-2} (ACD/Percepta 2012) 1.7×10^{-2} – 2.8×10^{-2} (VCCLab 2005)	8.3 (Exp) ^a

Substance (CAS RN)	Representative structure	Molecular weight (g/mol)	Water solubility (mg/L)	Octanol-water partition coefficient log K_{ow}
				
DIDP (26761-40-0/ 68515-49-1)	<p>trimethyl heptyl ester groups</p>  <p>dimethyl octyl ester groups</p>  <p>methyl nonyl ester groups</p> 	446	1.7×10^{-4} (Exp) ^e	<p>10.06–10.36 (KOWWIN 2010) 8.31–8.62 (WSKOWWIN)</p> <p>9.72–9.84 (ACD/Percepta 2012)</p>
DIUP (85507-79-5)	<p>dimethyl octyl ester groups</p>  <p>dimethyl nonyl ester groups</p> 	446–502	<p>2.8×10^{-8}– 2.9×10^{-7} (EpiSuite 2010) 8.9×10^{-4}– 2.9×10^{-3} (ACD/Percepta 2012) 9.9×10^{-3}– 1.2×10^{-2} (VCCLab 2005)</p>	<p>11.29–12.17 (EpiSuite 2010)</p> <p>10.48–11.66 (ACD/Percepta 2012)</p> <p>8.89–9.36 (VCCLab 2005)</p>

Substance (CAS RN)	Representative structure	Molecular weight (g/mol)	Water solubility (mg/L)	Octanol-water partition coefficient log K_{ow}
	 <p>dimethyl decyl ester groups</p> 			
DTDP (68515-47-9)	<p>dimethyl nonyl ester groups</p>  <p>dimethyl decyl ester groups</p>  <p>dimethyl undecyl ester groups</p>   <p>dimethyl dodecyl ester groups</p>	474 – 502	2.5×10^{-10} – 2.9×10^{-7} (WSKOWWIN 2010) 9.9×10^{-5} – 2.9×10^{-3} (ACD/Percepta 2012) 9.9×10^{-3} – 1.2×10^{-2} (VCCLab 2005)	11.19–14.14 (KOWWIN 2010) 10.48–14.3 (ACD/Percepta 2012) 8.89–10.17 (VCCLab 2005)

Substance (CAS RN)	Representative structure	Molecular weight (g/mol)	Water solubility (mg/L)	Octanol-water partition coefficient log K _{ow}
				
DUP (3648-20-2)		475	1.6 x 10 ⁻⁷ (EpiSuite 2010) 1.9 x 10 ⁻³ (ACD Percepta 2012) 1.7 x 10 ⁻² (VCCLab 2005)	8.7 (Exp) ^a

Abbreviations: (Exp), Experimental values

Experimental data obtained from ^a ECHA c2007-2015b; ^b HSDB 1983- ; ^c PhysProp 2006; ^d Haynes and Lide 2010; ^e Letinski et al. 2002; ^f ACC 2006; ^g European Commission 2000; ^h Renberg et al. 1985

Appendix B. Cumulative risk based on narcosis**Table B-1. Cumulative risk based on narcosis**

Substance (CAS RN)	PEC^a (µg/L)	BAF	Tissue residue^b (mmol/kg BW)	Toxic unit^c
DMP (131-11-3)	0.20	66	6.63×10^{-5}	0.002
DEP (84-66-2)	1.98	14	1.25×10^{-4}	0.003
DPrP (131-16-8)	0.03	17	2.33×10^{-6}	0.00006
DIBP (84-69-5)	0.13	78	3.61×10^{-5}	0.0009
DBP (84-74-2)	0.65	60	1.40×10^{-4}	0.004
CHIBP (5334-09-8)	NC	103	0	0.000
BCHP (84-64-0)	0.03	117	1.01×10^{-5}	0.0003
BBP (85-68-7)	1.95	631	3.95×10^{-3}	0.099
DCHP (84-61-7)	2.0	92	5.58×10^{-4}	0.014
DnHP (84-75-3)	0.007	262	5.58×10^{-6}	0.0001
DBzP (523-31-9)	0.01	17	5.56×10^{-7}	0.00001
B79P (68515-40-2)	3.61	31	3.04×10^{-4}	0.008
DMCHP (27987-25-3)	0.01	2070	6.03×10^{-5}	0.002
DIHepP (71888-89-6)	0.33	115	1.05×10^{-4}	0.003
79P (111381-89-6)	0.003	381	2.83×10^{-6}	0.00007
BIOP (27215-22-1)	0.008	47	9.85×10^{-7}	0.00002
DIOP (27554-26-3)	0.34	293	2.58×10^{-4}	0.006
DEHP (117-81-7)	1.41	41	1.47×10^{-4}	0.004
DINP (68515-48-0 / 28553-12-0)	3.43	28	2.29×10^{-4}	0.006
B84P	0.07	7	1.10×10^{-6}	0.00003

Substance (CAS RN)	PEC^a (µg/L)	BAF	Tissue residue^b (mmol/kg BW)	Toxic unit^c
(16883-83-3)				
610P (68648-93-1)	0.006	372	5.47×10^{-6}	0.0001
DnOP (117-84-0)	0.33	32	2.68×10^{-5}	0.0007
D911P (68515-43-5)	0.62	415	5.78×10^{-4}	0.014
D911P-2 (111381-91-0)	0.002	263	1.12×10^{-6}	0.00003
DIDP (26761-40-0 / 68515-49-1)	1.23	11	3.03×10^{-5}	0.0008
DIUP (85507-79-5)	0.044	10	9.18×10^{-7}	0.00002
DTDP (68515-47-9)	0.004	1	8.20×10^{-9}	0.0000
DUP (3648-20-2)	0.051	16	1.72×10^{-6}	0.00004
Sum of Internal Toxic Units	–	–	–	0.2

Abbreviations: PEC, predicted environmental concentration; BAF, bioaccumulation factor; ITUs, internal toxic units; ITU_{mix}, sum of internal toxic units for a mixture of substances; AF, assessment factor; NC, not calculated; –, not applicable

^a This PEC was calculated using a dilution factor based on 50th percentile flow, with no limit

^b The tissue residue is calculated by multiplying the PEC and BAF, and dividing by the molecular weight of the substance

^c Toxic units for each substance are calculated by dividing the tissue residue by a critical body residue of 0.2 mmol/kgBW and an assessment factor of 5.

Appendix B2. Analysis of cumulative risk based on narcosis

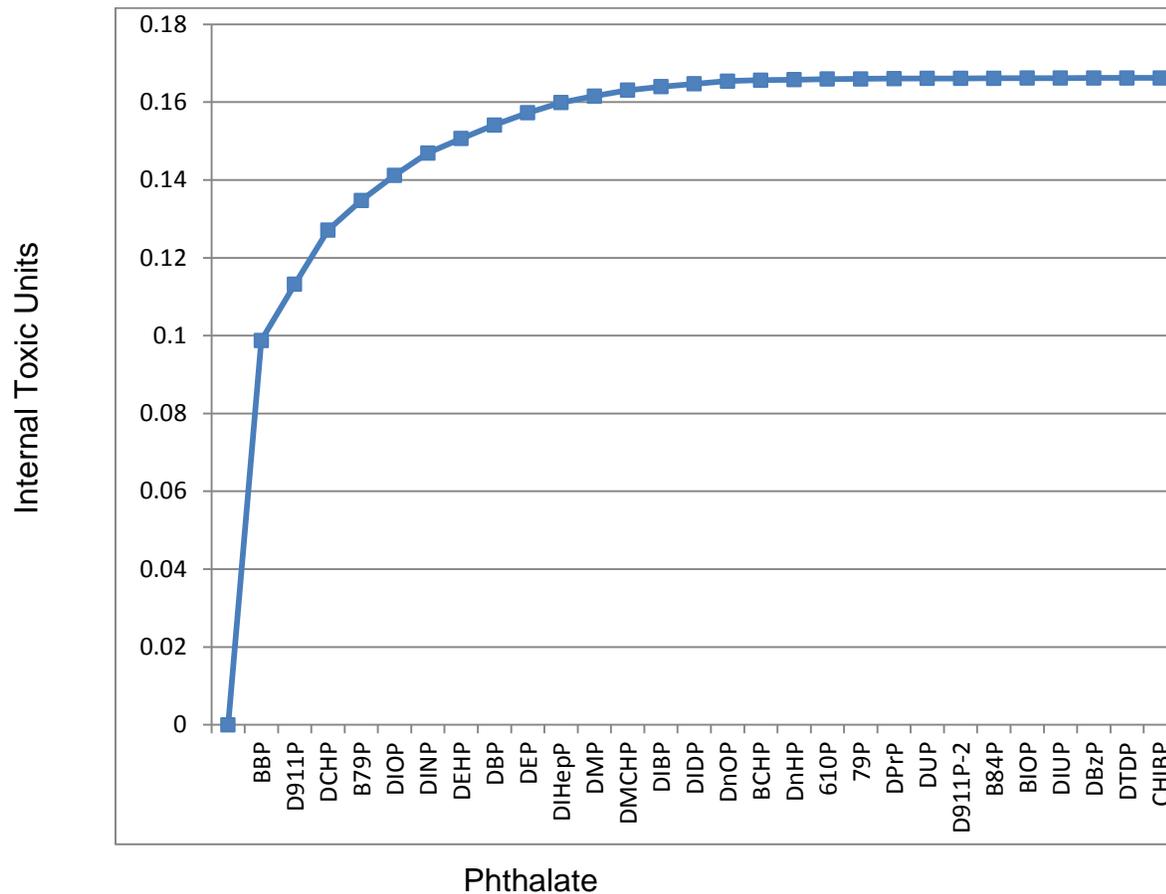


Figure B-1. Phthalate contributions to total toxic units based on narcosis

Ten phthalates account for approximately 95% of cumulative risk based on narcosis. Total Internal Toxic Units were calculated as 0.2.

Appendix C. Derivation of daily intakes for BBP, DBP and DEHP based on biomonitoring

MIREC, P4 and MIREC-CD Plus:

Estimating daily intake concentration using 1 metabolite concentration (BBP)

Equation 1:

$$\text{BBP daily intake} (\mu\text{g}/\text{kg bw. day}) = \frac{C_{\text{SUM}} \left(\frac{\text{moles}}{\text{g Cr}} \right) \times \text{CER} \times \text{MW of BBP}}{\text{FUE}_{\text{SUM}} \times \text{BW}}$$

Where $C_{\text{SUM}} \left(\frac{\text{moles}}{\text{g Cr}} \right)$ = Sum of molar concentrations of metabolites, CER: 24 hour creatinine excretion rate (estimated using the Mage Equation), FUE_{SUM} : Sum of fractional urinary excretion values of the metabolites = 0.73, MW of BBP = 312

Step 1: Conversion of concentrations

$$C_{\text{metabolite}} \left(\frac{\text{moles}}{\text{g Cr}} \right) = \frac{C_{\text{metabolite}} (\mu\text{g}/\text{g Cr})}{\text{MW}_{\text{metabolite}}}$$

$$C_{\text{MBzP}} \left(\frac{\text{moles}}{\text{g Cr}} \right) = \frac{C_{\text{Metabolite}} (\mu\text{g}/\text{g Cr})}{256 \text{ g/mol}}$$

Step 2: Identify relevant FUE

FUE for MBzP is 0.73

Step 3: Compute DI for BBP using Equation 1.

Estimating daily intake concentration using multiple metabolite concentrations (DBP and DEHP)

Equation 1:

$$\text{Phthalate daily intake} (\mu\text{g}/\text{kg bw. day}) = \frac{C_{\text{SUM}} \left(\frac{\text{moles}}{\text{g Cr}} \right) \times \text{CER} \times \text{MW of phthalate}}{\text{FUE}_{\text{SUM}} \times \text{BW}}$$

Where $C_{\text{SUM}} \left(\frac{\text{moles}}{\text{g Cr}} \right)$ = Sum of molar concentrations of metabolites, CER: 24 hour creatinine excretion rate (estimated using the Mage Equation), FUE_{SUM} : Sum of FUE of the metabolites = 0.91 (DBP), 0.71 (DEHP), MW of phthalate = 278 (DBP), 391 (DEHP)

Step 1: Converting the urinary metabolite concentration from $\mu\text{g}/\text{g Cr}$ to $\text{moles}/\text{g Cr}$

$$C_{\text{metabolite}} \left(\frac{\text{moles}}{\text{g Cr}} \right) = \frac{C_{\text{metabolite Cr}} (\mu\text{g/g Cr})}{MW_{\text{metabolite}}}$$

I. For DBP metabolites: MnBP and MHBP¹⁶

$$C_{\text{MnBP}} \left(\frac{\text{moles}}{\text{g Cr}} \right) = \frac{UC_{\text{MnBP Cr}} (\mu\text{g/g Cr})}{222 \text{ g/mol}}$$

$$C_{\text{MHBP}} \left(\frac{\text{moles}}{\text{g Cr}} \right) = \frac{UC_{\text{MHBP Cr}} (\mu\text{g/g Cr})}{238 \text{ g/mol}}$$

Step 2: Sum the metabolite concentration (moles/g Cr) from Step 1¹⁷

II. For DEHP metabolites: MEHP, MEOHP, MEHHP, MCMHP, MECPP

$$C_{\text{MEHP}} \left(\frac{\text{moles}}{\text{g Cr}} \right) = \frac{UC_{\text{MEHP Cr}} (\mu\text{g/g Cr})}{278 \text{ g/mol}}$$

$$C_{\text{MEOHP}} \left(\frac{\text{moles}}{\text{g Cr}} \right) = \frac{UC_{\text{MEOHP Cr}} (\mu\text{g/g Cr})}{292 \text{ g/mol}}$$

$$C_{\text{MEHHP}} \left(\frac{\text{moles}}{\text{g Cr}} \right) = \frac{UC_{\text{MEHHP Cr}} (\mu\text{g/g Cr})}{294 \text{ g/mol}}$$

$$C_{\text{MCMHP}} \left(\frac{\text{moles}}{\text{g Cr}} \right) = \frac{UC_{\text{MCMHP Cr}} (\mu\text{g/g Cr})}{308 \text{ g/mol}}$$

$$C_{\text{MECPP}} \left(\frac{\text{moles}}{\text{g Cr}} \right) = \frac{UC_{\text{MECPP Cr}} (\mu\text{g/g Cr})}{308 \text{ g/mol}}$$

Step 2: Sum the metabolite concentration (moles/g Cr) from Step 1

I. For DBP metabolites in step 1

$$C_{\text{SUM}} \left(\frac{\text{moles}}{\text{g Cr}} \right) = \Sigma C_{\text{MnBP}} + C_{\text{MHBP}}$$

¹⁶ P4 and MIREC-CD plus data measured 2 metabolites of DBP (MnBP and MHBP). MIREC pregnant women measured 1 metabolite of DBP (MnBP).

¹⁷ P4 and MIREC-CD plus data measured 5 metabolites of DEHP (MEHP, MEOHP, MEHHP, MCMHP, MECPP). MIREC pregnant women measured 3 metabolites of DEHP (MEHP, MEOHP, MEHHP).

II. For DEHP metabolites in step 1

$$C_{SUM} \left(\frac{\text{moles}}{\text{g Cr}} \right) = \Sigma C_{MEHP} + C_{MEOHP} + C_{MEHHP} + C_{MCMHP} + C_{MECPP}$$

Step 3: Calculate the sum of FUEs.

- I. DBP: FUEs for MnBP and MHBP are 0.84 and 0.069, respectively. Therefore, the sum would be 0.91 (P4 and MIREC-CD Plus) and the FUE for only MnBP is 0.84 (MIREC).
- II. DEHP: FUEs are MEHP (0.073), MEOHP (0.15), MEHHP (294), MCMHP (0.038) and MECPP (0.21). Therefore, the sum of all 5 metabolites would be 0.71 (P4 and MIREC-CD Plus) and the sum of the first 3 would be 0.46 (MIREC).

Step 4: Compute the daily intake using Equation 1.

CHMS

Statistical analysis: The data were analyzed with SAS 9.2 (SAS Institute Inc., USA) and SUDAAN 10.0.1 software (RTI International, USA). Variance estimates were produced using bootstrap weights, taking into account the 11 degrees of freedom for cycle 1 and 13 degrees of freedom for cycle 2 as suggested in CHMS data user guide. All analyses were weighted using the CHMS cycle 1 survey weights (phthalates sub-sample) and CHMS cycle 2 survey weights (environmental urine subsample) in order to be representative of the Canadian population. Phthalate concentrations that were below LOD were assigned a value of LOD/2.

Estimation of creatinine excretion rate (CER): For each study, participant creatinine excretion rate was calculated using the Mage equations (from (15)). The adiposity adjustment (discussed in the supplemental information (15)) was applied for all participants, and the body surface area adjustment was applied for children under the age of 18. Median BMIs by age for the adiposity adjustment were computed using the entire CHMS sample. The CHMS phthalate subsample dataset had 174 children who exceeded the height limits in the Mage equations (186 cm for males and 172 cm for females). The Mage equations were applied directly to the observed heights in order to extrapolate creatinine excretion rates for these participants. The predicted excretion rates for these individuals appeared to be reasonable despite the extrapolation.

Estimation of urinary excretion rate: For each selected phthalate, the urinary excretion rate was calculated using CER as follows

$$UER (\mu g/kg BW/day) = \frac{UC_{Cr} \left(\frac{\mu g}{g Cr} \right) \times CER \left(\frac{g}{day} \right)}{BW (kg)} \quad \text{Equation 1}$$

UER is the body-weight adjusted urinary excretion rate. The UC_{Cr} is the creatinine-adjusted urinary phthalate concentration, and BW refers to the body-weight. The UER for individual participants were computed and used in the regression model (see below) to derive least square geometric mean (LSGM) estimates of UER for the Canadian population.

Daily intake estimation: The daily intake of each phthalate was estimated for each participant using the following equations (David et al. 2000; Koch et al. 2007):

$$\text{Daily intake } (\mu g/kg BW/day) = \frac{UER \left(\frac{\mu g}{day \times kg BW} \right)}{FUE} \times \frac{MW_D}{MW_M} \quad \text{Equation 2}$$

The fractional urinary excretion (FUE) is defined as the fraction of the diester exposure dose excreted as monoesters in urine, calculated on mole-basis. For the daily intake estimations, previous works used FUE values of 0.73, 0.44, and 0.69 for BBP, DEHP, and DBP respectively (19, 21, 25; Koch et al. 2012). MW_D and MW_M are the molecular weights of the diester (312.36, 390.56, and 278.34 g/mole for BBP, DEHP, and DBP respectively) and the monoester (256.22, 865.02, and 222.24 g/mole for BBP, MEHP+MEHHP+MEOHP, and MBP) respectively.

For each selected phthalate diester, the daily intake for each study participants was computed using equation 2. Arithmetic and geometric means and selected percentiles along with their 95% confidence intervals of daily intake were produced for the Canadian population by age groups, sex and fasting status. Descriptive statistics were computed using SUDAAN proc DESCRIPT and SAS proc SURVEYREG.

Appendix D. Intakes of BBP, DBP, DEHP, DnHP and DIOP from environmental media and food for the general population

Table D-1a. Central tendency and (upper-bounding) estimates of daily intake of BBP by various age groups (µg/kg bw/day)

Route of exposure	0–0.5 year ^a	0–0.5 year ^a	0–0.5 year ^a	0.5–4 years ^d	5–11 years ^e	12–19 years ^f	20–59 years ^g	60+ years ^h
	Breast-fed ^b	Formula-fed ^c	Not formula-fed					
Ambient air ⁱ	< 0.001	< 0.001	< 0.001	< 0.001	< 0.001	< 0.001	< 0.001	< 0.001
Indoor air ^j	< 0.001 (0.006)	< 0.001 (0.006)	< 0.001 (0.006)	0.001 (0.013)	0.001 (0.0101)	< 0.001 (0.005)	< 0.001 (0.004)	< 0.001 (0.004)
Drinking water ^k	N/A	0.0045	0.0017	0.0019	0.0015	< 0.001	< 0.001	< 0.001
Food and beverages ^l	< 0.001 (0.016)	< 0.001	NA	0.43 (1.16)	0.25 (0.61)	0.15 (0.45)	0.069 (0.22)	0.049 (0.17)
Soil ^m	< 0.001	< 0.001	< 0.001	< 0.001	< 0.001	< 0.001	< 0.001	< 0.001
Dust ⁿ	0.21 (2.59)	0.21 (2.59)	0.21 (2.59)	0.15 (1.82)	0.071 (0.86)	0.0026 (0.031)	0.0025 (0.029)	0.0024 (0.028)
Total oral intake	0.21 (2.61)	0.21 (2.60)	0.21 (2.60)	0.58 (2.99)	0.33 (1.48)	0.15 (0.49)	0.072 (0.25)	0.051 (0.20)

Abbreviations: [NA, Not Available; N/A, Not Applicable]

- ^a Assumed to weigh 7.5 kg, to breathe 2.1 m³ of air per day, to drink 0.2 L/day (not formula-fed) and to ingest 30 mg of soil per day. Consumption of food groups reported in Health Canada (1998). Median and 95th percentile dietary intake estimates (food) for the < 6 months age group, as presented in Table D-1b, were used to represent dietary intake for this age group (applicable to formula- and non-formula-fed group).
- ^b Infants 0-6 months assumed to ingest 0.742 litre breast milk/day (USEPA 2011). MBzP the monoester metabolite of BBP was measured in breast milk in Canada as part of the Plastics and Personal Care Product Use in Pregnancy survey (P4, n = 31 women, 56 breast milk samples; personal communication from Environmental Health Science and Radiation Directorate [EHSRD] to ESRAB, October 2013; unreferenced). It was detected in 34% of samples, with half the limit of detection (LOD) (LOD=0.018 µg/L) and maximum (0.16 µg/L) used for exposure characterization.
- ^c Probabilistic intakes (median and 90th) were incorporated into the dietary intake table. Formula concentrations obtained from P4 study – BBP was not detected in any infant formula samples: one half the limit of detection (LOD=0.018 µg/L) was used for exposure characterization.
- ^d Assumed to weigh 15.5 kg, to breathe 9.3 m³ of air per day, to drink 0.7 L of water per day and to ingest 100 mg of soil per day. Consumption of food groups reported in Health Canada (1998). Median and 95th percentile dietary intake estimates (food) for the 1–3-year age group, as presented in Table D-1b, were used to represent dietary intake for this age group.
- ^e Assumed to weigh 31.0 kg, to breathe 14.5 m³ of air per day, to drink 1.1 L of water per day and to ingest 65 mg of soil per day. Consumption of food groups reported in Health Canada (1998). Median and 95th percentile dietary intake estimates (food) for the 4–8-year age group, as presented in Table D-1b, were used to represent dietary intake for this age group.
- ^f Assumed to weigh 59.4 kg, to breathe 15.8 m³ of air per day, to drink 1.2 L of water per day and to ingest 30 mg of soil per day. Consumption of food groups reported in Health Canada (1998). Highest median and 95th percentile dietary intake estimates (food) for the 9–13-year age group, as presented in Table D-1b, were used to represent dietary intake for this age group.
- ^g Assumed to weigh 70.9 kg, to breathe 16.2 m³ of air per day, to drink 1.5 L of water per day and to ingest 30 mg of soil per day. Consumption of food groups reported in Health Canada (1998). Highest median and 95th percentile dietary intake estimates (food) for the 19–30-year age group, as presented in Table D-1b, were used to represent dietary intake for this age group.

- ^h Assumed to weigh 72.0 kg, to breathe 14.3 m³ of air per day, to drink 1.6 L of water per day and to ingest 30 mg of soil per day. Consumption of food groups reported in Health Canada (1998). Highest median and 95th percentile dietary intake estimates (food) for the 71-year-old and over age group, as presented in Table D-1b, were used to represent dietary intake for this age group.
- ⁱ No Canadian data measuring BBP in ambient air were identified. Rudel et al. 2010 measured BBP in outdoor samples (40 homes) in N. California. Concentrations used in exposure characterization –half the method reporting limit (MRL=0.006 µg/m³), maximum: 0.0085 µg/m³.
- ^j No Canadian data measuring BBP in indoor air were identified. Tran and Kannan 2015 measured BBP in (20 homes) in Albany, NY, USA. Median (0.00299 µg/m³) and maximum (0.0247 µg/m³) concentrations were used in exposure characterization.
- ^k No data were identified regarding BBP concentrations in drinking water. BBP was not detected in any samples in a Canadian bottled water survey (Cao 2008). Half the method detection limit (MDL=0.085 µg/L) was used for semi-quantitative exposure characterization.
- ^l Probabilistic intakes (median and 95th) were incorporated into the dietary intake table. Intakes and methodology are outlined in Appendix E (see Table D-1b). Note gender and age groups do not fully match; therefore, the highest intake from within an age group was input into the table: e.g., male intakes (51–70 years) were input into the 60+ (unisex) column because this age group had the highest intake of all the groups in the 51–71-year range. NA, notates significant variation; therefore, estimates not presented.
- ^m The reported concentration of BBP in control agricultural soils (0.13 ng/g; Khosravi and Price 2015) was used to estimate potential exposures to BBP via soil.
- ⁿ The ingestion of indoor dust is considered a significant source of indoor exposure to phthalates, including BBP, and the amount of indoor dust ingested each day is based on Wilson et al. (2013). The median (42.3 µg/g) and 95th percentile (512 µg/g) of BBP in indoor dust, was used for exposure characterization (Kubwabo et al. 2013).

Table D-1b. Probabilistic estimates of daily intake of BBP from food (µg/kg bw/day)

DRI group	Median	95th percentile
< 6 months	NA	NA
0.5–1 year	NA	1.27
1–3 years	0.43	1.16
4–8 years	0.25	0.61
M: 9–13 years	0.15	0.45
F: 9–13 years	0.12	0.35
M: 14–18 years	0.11	0.32
F: 14–18 years	0.0798	0.27
M: 19–30 years	0.0692	0.22
F: 19–30 years	0.0646	0.22
M: 31–50 years	0.0509	0.17
F: 31–50 years	0.052	0.18
M: 51–70 years	0.0452	0.15
F: 51–70 years	0.0448	0.15
M: > 71 years	0.047	NA
F: > 71 years	0.049	0.17

NA; not available because of high cumulative variation

Table D-2a. Central tendency and (upper-bounding) estimates of daily intake of DBP by various age groups (µg/kg bw/day)

Route of exposure	0–0.5 year ^a	0–0.5 year ^a	0–0.5 year ^a	0.5–4 years ^d	5–11 years ^e	12–19 years ^f	20–59 years ^g	60+ years ^h
	Breast fed ^b	Formula-fed ^c	Not formula-fed					
Ambient air ⁱ	< 0.001 (0.0012)	< 0.001 (0.0012)	< 0.001 (0.0012)	< 0.001 (0.0024)	< 0.001 (0.0019)	< 0.001 (0.0011)	< 0.001	< 0.001
Indoor air ^j	0.049 (0.27)	0.049 (0.27)	0.049 (0.27)	0.11 (0.58)	0.082 (0.45)	0.046 (0.26)	0.040 (0.22)	0.035 (0.19)
Drinking water ^k	N/A	0.038 (0.18)	0.014 (0.069)	0.016 (0.078)	0.013 (0.061)	0.0072 (0.035)	0.0075 (0.036)	0.0079 (0.038)
Food and beverages ^l	0.065 (0.51)	NA	NA	0.69 (1.96)	0.47 (1.16)	0.30 (0.93)	0.14 (0.44)	0.12 (0.38)
Soil ^m	< 0.001	< 0.001	< 0.001	< 0.001	< 0.001	< 0.001	< 0.001	< 0.001
Dust ⁿ	0.085 (0.48)	0.085 (0.48)	0.085 (0.48)	0.060 (0.34)	0.028 (0.16)	0.001 (0.006)	<0.001 (0.005)	<0.001 (0.005)
Total oral intake	0.199 (1.53)	0.18 (0.95)	0.15 (0.82)	0.88 (2.96)	0.59 (1.83)	0.35 (1.23)	0.19 (0.70)	0.16 (0.61)

Abbreviations: [NA, Not Available; N/A, Not Applicable]

- ^a Assumed to weigh 7.5 kg, to breathe 2.1 m³ of air per day, to drink 0.2 L/day (not formula-fed) and to ingest 30 mg of soil per day. Consumption of food groups reported in Health Canada (1998). Median and 95th percentile dietary intake estimates (food) for the < 6 months age group, as presented in Table D-2b, were used to represent dietary intake for this age group (applicable to formula- and non-formula-fed group).
- ^b Infants 0-6 months assumed to ingest 0.742 litre breast milk/day (USEPA 2011). MBzP the monoester metabolite of DBP was measured in breast milk in Canada as part of the Plastics and Personal Care Product Use in Pregnancy survey (P4, n = 31 women, 56 breast milk samples; personal communication from Environmental Health Science and Radiation Directorate [EHSRD] to ESRAB, October 2013). It was detected in 100% of breast milk samples, with median (0.656 µg/L) and maximum (5.18 µg/L) values used for exposure characterization.
- ^c Probabilistic intakes (median and 90th) were incorporated into the dietary intake table. Intakes and methodology are outlined in Appendix E (see Table D-2b). NA, notates significant variation; therefore, estimates not presented.
- ^d Assumed to weigh 15.5 kg, to breathe 9.3 m³ of air per day, to drink 0.7 L of water per day and to ingest 100 mg of soil per day. Consumption of food groups reported in Health Canada (1998). Median and 95th percentile dietary intake estimates (food) for the 1–3-year age group, as presented in Table D-2b, were used to represent dietary intake for this age group.
- ^e Assumed to weigh 31.0 kg, to breathe 14.5 m³ of air per day, to drink 1.1 L of water per day and to ingest 65 mg of soil per day. Consumption of food groups reported in Health Canada (1998). Median and 95th percentile dietary intake estimates (food) for the 4–8-year age group, as presented in Table D-2b, were used to represent dietary intake for this age group.
- ^f Assumed to weigh 59.4 kg, to breathe 15.8 m³ of air per day, to drink 1.2 L of water per day and to ingest 30 mg of soil per day. Consumption of food groups reported in Health Canada (1998). Highest median and 90th percentile dietary intake estimates (food) for the 9–13-year age group, as presented in Table D-2b, were used to represent dietary intake for this age group.
- ^g Assumed to weigh 70.9 kg, to breathe 16.2 m³ of air per day, to drink 1.5 L of water per day and to ingest 30 mg of soil per day. Consumption of food groups reported in Health Canada (1998). Highest median and 95th percentile dietary intake estimates (food) for the 19–30-year age group, as presented in Table D-2b, were used to represent dietary intake for this age group.
- ^h Assumed to weigh 72.0 kg, to breathe 14.3 m³ of air per day, to drink 1.6 L of water per day and to ingest 30 mg of soil per day. Consumption of food groups reported in Health Canada (1998). Highest median and 95th percentile dietary intake estimates (food) for the 71-year-old and over age group, as presented in Table D-2b, were used to represent dietary intake for this age group.

- ⁱ No Canadian data measuring DBP in ambient air were identified. Rudel et al. 2010 measured DBP in outdoor samples (40 homes) in N. California. Concentrations used in exposure characterization –half the method reporting limit (MRL=0.007 µg/m³), maximum: 0.032 µg/m³.
- ^j Zhu et al. 2007 measured DBP in indoor air from samples collected in homes in Canada. Median (0.2 µg/m³) and maximum (1.1 µg/m³) concentrations were used in exposure characterization (Zhu et al. 2007).
- ^k No data were identified regarding DBP concentrations in drinking water. In the absence of data on levels of DBP in tap water, mean (0.357 µg/L) and maximum (1.72 µg/L) concentrations of DBP in bottled non-carbonated water were used for semi-quantitative exposure characterization (Cao et al. 2008).
- ^l Probabilistic intakes (median and 95th) were incorporated into the dietary intake table. Intakes and methodology are outlined in Appendix E (see Table D-2b). Note gender and age groups do not fully match; therefore, the highest intake from within an age group was input into the table: e.g., male intakes (51–70 years) were input into the 60+ (unisex) column because this age group had the highest intake of all the groups in the 51–71-year range. NA, notates significant variation; therefore, estimates not presented.
- ^m The reported concentration of DBP in control agricultural soils (0.14 ng/g; Khosravi and Price 2015) was used to estimate potential exposures to DBP via soil.
- ⁿ The ingestion of indoor dust is considered a significant source of indoor exposure to phthalates, including DBP, and the amount of indoor dust ingested each day is based on Wilson et al. (2013). The median (16.8 µg/g) and 95th percentile (95.4 µg/g) of DBP in indoor dust, was used for exposure characterization (Kubwabo et al. 2013).

Table D-2b. Probabilistic estimates of daily intake of DBP from food (µg/kg bw/day)

DRI group	Median	95th percentile
< 6 months	NA	NA
0.5–1 year	NA	NA
1–3 years	0.69	1.96
4–8 years	0.47	1.16
M: 9–13 years	0.30	0.93
F: 9–13 years	0.26	0.71
M: 14–18 years	0.21	0.65
F: 14–18 years	0.18	0.53
M: 19–30 years	0.14	0.44
F: 19–30 years	0.14	0.42
M: 31–50 years	0.13	0.37
F: 31–50 years	0.13	0.39
M: 51–70 years	0.12	0.35
F: 51–70 years	0.12	0.36
M: > 71 years	0.12	0.36
F: > 71 years	0.12	0.38

NA; not available because of high cumulative variation

Table D-3a. Central tendency and (upper-bounding) estimates of daily intake of DEHP by various age groups (µg/kg bw/day)

Route of exposure	0–0.5 year ^a	0–0.5 year ^a	0–0.5 year ^a	0.5–4 years ^d	5–11 years ^e	12–19 years ^f	20–59 years ^g	60+ years ^h
	Breast fed ^b	Formula-fed ^c	Not formula-fed					
Ambient air ⁱ	< 0.001	< 0.001	< 0.001	0.0015 (0.0017)	0.0012 (0.0013)	< 0.001	< 0.001	< 0.001
Indoor air ^j	0.022 (0.52)	0.022 (0.52)	0.022 (0.52)	0.046 (1.10)	0.036 (0.86)	0.021 (0.49)	0.018 (0.42)	0.015 (0.37)
Drinking water ^k	N/A	0.011 (0.036)	0.0041 (0.014)	0.0046 (0.015)	0.0036 (0.012)	0.0021 (0.0068)	0.0022 (0.0072)	0.0023 (0.0075)
Food and beverages ^l	0.13 (1.69)	NA	5.59 (17.24)	8.76 (19.78)	5.55 (13.58)	3.45 (9.49)	2.19 (6.14)	2.19 (6.14)
Soil ^m	< 0.001	< 0.001	< 0.001	< 0.001	< 0.001	< 0.001	< 0.001	< 0.001
Dust ⁿ	2.34 (9.53)	2.34 (9.53)	2.34 (9.53)	1.64 (6.67)	0.77 (3.15)	0.028 (0.11)	0.027 (0.11)	0.026 (0.10)
Total oral intake	2.49 (11.74)	2.39 (10.31)	7.96 (27.30)	10.45 (27.57)	6.36 (17.60)	3.5 (10.10)	2.24 (6.68)	2.23 (6.62)

Abbreviations: [NA, Not Available; N/A, Not Applicable]

- ^a Assumed to weigh 7.5 kg, to breathe 2.1 m³ of air per day, to drink 0.2 L/day (not formula-fed) and to ingest 30 mg of soil per day. Consumption of food groups reported in Health Canada (1998). Median and 95th percentile dietary intake estimates (food) for the 0.5–1-year age group, as presented in Table D-3b, were used to represent dietary intake for this age group (applicable to formula- and non-formula-fed group).
- ^b Infants 0-6 months assumed to ingest 0.742 litre breast milk/day (USEPA 2011). MEHP the monoester metabolite of DEHP was measured in breast milk in Canada as part of the Plastics and Personal Care Product Use in Pregnancy survey (P4, n = 31 women, 56 breast milk samples; personal communication from Environmental Health Science and Radiation Directorate [EHSRD] to ESRAB, October 2013). It was detected in 100% of samples, with median (1.26 µg/L) and maximum (17.05 µg/L) used for exposure characterization.
- ^c Probabilistic intakes (median and 90th) were incorporated into the dietary intake table. Intakes and methodology are outlined in Appendix E (see Table D-3b). NA, notates significant variation; therefore, estimates not presented.
- ^d Assumed to weigh 15.5 kg, to breathe 9.3 m³ of air per day, to drink 0.7 L of water per day and to ingest 100 mg of soil per day. Consumption of food groups reported in Health Canada (1998). Median and 95th percentile dietary intake estimates (food) for the 1–3-year age group, as presented in Table D-3b, were used to represent dietary intake for this age group.
- ^e Assumed to weigh 31.0 kg, to breathe 14.5 m³ of air per day, to drink 1.1 L of water per day and to ingest 65 mg of soil per day. Consumption of food groups reported in Health Canada (1998). Median and 95th percentile dietary intake estimates (food) for the 4–8-year age group, as presented in Table D-3b, were used to represent dietary intake for this age group.
- ^f Assumed to weigh 59.4 kg, to breathe 15.8 m³ of air per day, to drink 1.2 L of water per day and to ingest 30 mg of soil per day. Consumption of food groups reported in Health Canada (1998). Highest median and 95th percentile dietary intake estimates (food) for the 9–13-year age group, as presented in Table D-3b, were used to represent dietary intake for this age group.
- ^g Assumed to weigh 70.9 kg, to breathe 16.2 m³ of air per day, to drink 1.5 L of water per day and to ingest 30 mg of soil per day. Consumption of food groups reported in Health Canada (1998). Highest median and 95th percentile dietary intake estimates (food) for the 51–70-year age group, as presented in Table D-3b, were used to represent dietary intake for this age group.
- ^h Assumed to weigh 72.0 kg, to breathe 14.3 m³ of air per day, to drink 1.6 L of water per day and to ingest 30 mg of soil per day. Consumption of food groups reported in Health Canada (1998). Highest median and 95th percentile dietary intake estimates (food) for the 51–70-year age group, as presented in Table D-3b, were used to represent dietary intake for this age group.

- ⁱ No Canadian data measuring DEHP in ambient air were identified. Rudel et al. 2010 measured DEHP in outdoor samples (40 homes) in N. California. Concentrations used in exposure characterization –half the method reporting limit (MRL=0.040 µg/m³), maximum: 0.023 µg/m³.
- ^j Zhu et al. 2007 measured DEHP in indoor air from samples collected in homes in Canada. Median (0.088 µg/m³) and maximum (2.1 µg/m³) concentrations were used in exposure characterization (Zhu et al. 2007).
- ^k No data were identified regarding DEHP concentrations in drinking water. In the absence of data on levels of DEHP in tap water, mean (0.102µg/L) and maximum (0.338 µg/L) concentrations of DEHP in bottled non-carbonated water were used for semi-quantitative exposure characterization (Cao et al. 2008).
- ^l Probabilistic intakes (median and 95th) were incorporated into the dietary intake table. Intakes and methodology are outlined in Appendix E (see Table D-3b). Note gender and age groups do not fully match; therefore, the highest intake from within an age group was input into the table: e.g., male intakes (51–70 years) were input into the 60+ (unisex) column because this age group had the highest intake of all the groups in the 51–71-year range. NA, notates significant variation; therefore, estimates not presented.
- ^m The reported concentration of DEHP in control agricultural soils (0.06 ng/g; Khosravi and Price 2015) was used to estimate potential exposures to DEHP via soil.
- ⁿ The ingestion of indoor dust is considered a significant source of indoor exposure to phthalates, including DEHP, and the amount of indoor dust ingested each day is based on Wilson et al. (2013). The median (462 µg/g) and 95th percentile (1880 µg/g) of DEHP in indoor dust, was used for exposure characterization (Kubwabo et al. 2013).

Table D-3b. Probabilistic estimates of daily intake of DEHP from food (µg/kg bw/day)

DRI group	Median	95th percentile
< 6 months	NA	NA
0.5–1 year	5.59	17.24
1–3 years	8.76	19.78
4–8 years	5.55	13.58
M: 9–13 years	3.45	9.49
F: 9–13 years	3.23	9.19
M: 14–18 years	2.30	6.54
F: 14–18 years	2.12	6.20
M: 19–30 years	1.88	5.97
F: 19–30 years	2.12	6.06
M: 31–50 years	1.96	5.64
F: 31–50 years	2.18	6.03
M: 51–70 years	2.04	5.48
F: 51–70 years	2.19	6.14
M: > 71 years	2.02	5.30
F: > 71 years	2.17	5.05

NA; not available because of high cumulative variation

Table D-4a. Central tendency and (upper-bounding) estimates of daily intake of DnHP by various age groups (µg/kg bw/day)

Route of exposure	0–0.5 year ^a Breast fed ^b	0–0.5 year ^a Formula-fed ^c	0–0.5 year ^a Not formula-fed	0.5–4 years ^d	5–11 years ^e	12–19 years ^f	20–59 years ^g	60+ years ^h
Food and beverages ⁱ	NA	NA	NA	0.0015 (0.037)	0.0016 (0.036)	0.001 (0.027)	< 0.001 (0.015)	< 0.001 (0.012)
Dust ^j	0.019 (0.31)	0.019 (0.31)	0.019 (0.31)	0.013 (0.22)	0.0064 (0.10)	< 0.001 (0.0038)	< 0.001 (0.0036)	< 0.001 (0.0034)
Total oral intake	0.019 (0.31)	0.019 (0.31)	0.019 (0.31)	0.015 (0.26)	0.008 (0.136)	0.001 (0.031)	< 0.001 (0.019)	< 0.001 (0.015)

^a Assumed to weigh 7.5 kg, to breathe 2.1 m³ of air per day, to drink 0.2 L/day (not formula-fed) and to ingest 30 mg of soil per day. Consumption of food groups reported in Health Canada (1998). Median and 90th percentile dietary intake estimates (food) for the < 6 months age group, as presented in Table D-4b, were used to represent dietary intake for this age group (applicable to formula- and non-formula-fed group).

^b No data on the levels of DnHP in breast milk were identified in Canada or elsewhere.

^c No data on the levels of DnHP in infant formula were identified in Canada or elsewhere. Probabilistic intakes (median and 90th) were incorporated into the dietary intake table. However, the daily intakes for the <1 year age groups were unreliable and were not reported.

^d Assumed to weigh 15.5 kg, to breathe 9.3 m³ of air per day, to drink 0.7 L of water per day and to ingest 100 mg of soil per day. Consumption of food groups reported in Health Canada (1998). Median and 90th percentile dietary intake estimates (food) for the 1–3-year age group, as presented in Table D-4b, were used to represent dietary intake for this age group.

^e Assumed to weigh 31.0 kg, to breathe 14.5 m³ of air per day, to drink 1.1 L of water per day and to ingest 65 mg of soil per day. Consumption of food groups reported in Health Canada (1998). Median and 90th percentile dietary intake estimates (food) for the 4–8-year age group, as presented in Table D-4b, were used to represent dietary intake for this age group.

^f Assumed to weigh 59.4 kg, to breathe 15.8 m³ of air per day, to drink 1.2 L of water per day and to ingest 30 mg of soil per day. Consumption of food groups reported in Health Canada (1998). Highest median and 90th percentile dietary intake estimates (food) for the 9–13-year age group, as presented in Table D-4b, were used to represent dietary intake for this age group.

^g Assumed to weigh 70.9 kg, to breathe 16.2 m³ of air per day, to drink 1.5 L of water per day and to ingest 30 mg of soil per day. Consumption of food groups reported in Health Canada (1998). Highest median and 90th percentile dietary intake estimates (food) for the 19–30-year age group, as presented in Table D-4b, were used to represent dietary intake for this age group.

^h Assumed to weigh 72.0 kg, to breathe 14.3 m³ of air per day, to drink 1.6 L of water per day and to ingest 30 mg of soil per day. Consumption of food groups reported in Health Canada (1998). Highest median and 90th percentile dietary intake estimates (food) for the 51–70-year age group, as presented in Table D-4b, were used to represent dietary intake for this age group.

ⁱ Probabilistic intakes (median and 90th) were incorporated into the dietary intake table. Intakes and methodology are outlined in Appendix E (see Table D-4b). Note gender and age groups do not fully match; therefore, the highest intake from within an age group was input into the table: e.g., male intakes (51–70 years) were input into the 60+ (unisex) column because this age group had the highest intake of all the groups in the 51–71-year range. NA, notates significant variation; therefore, estimates not presented.

^j The ingestion of indoor dust is considered a significant source of indoor exposure to phthalates, including DnHP, and the amount of indoor dust ingested each day is based on Wilson et al. (2013). The median (3.8 µg/g) and 95th percentile (62 µg/g) of DnHP in indoor dust, was used for exposure characterization (Kubwabo et al. 2013).

Table D-4b. Probabilistic estimates of daily intake of DnHP from food (µg/kg bw/day)

DRI group	Median	90th percentile
< 6 months	NA	NA
0.5–1 year	NA	NA
1–3 years	0.0015	0.037
4–8 years	0.0016	0.036
M: 9–13 years	0.001	0.027
F: 9–13 years	0.0009	0.023
M: 14–18 years	0.0008	0.020
F: 14–18 years	0.0005	0.013
M: 19–30 years	0.0007	0.015
F: 19–30 years	0.0004	0.010
M: 31–50 years	0.0006	0.012
F: 31–50 years	0.0004	0.0095
M: 51–70 years	0.0005	0.012
F: 51–70 years	0.0004	0.009
M: > 71 years	0.0005	0.011
F: > 71 years	0.0005	0.009

NA; not available because of high cumulative variation

Table D-5. Central tendency and (upper-bounding) estimates of daily intake of DIOP by various age groups (µg/kg bw/day)

Route of exposure	0–0.5 year^a	0.5–4 years^b	5–11 years^c	12–19 years^d	20–59 years^e	60+ years^f
Dust ^g	0.033 (0.14)	0.023 (0.099)	0.011 (0.047)	<0.001 (0.0017)	<0.001 (0.0016)	<0.001 (0.0015)

^a Assumed to weigh 7.5 kg, to breathe 2.1 m³ of air per day, to drink 0.2 L/day (not formula-fed) and to ingest 30 mg of soil per day.

^b Assumed to weigh 15.5 kg, to breathe 9.3 m³ of air per day, to drink 0.7 L of water per day and to ingest 100 mg of soil per day.

^c Assumed to weigh 31.0 kg, to breathe 14.5 m³ of air per day, to drink 1.1 L of water per day and to ingest 65 mg of soil per day.

^d Assumed to weigh 59.4 kg, to breathe 15.8 m³ of air per day, to drink 1.2 L of water per day and to ingest 30 mg of soil per day.

^e Assumed to weigh 70.9 kg, to breathe 16.2 m³ of air per day, to drink 1.5 L of water per day and to ingest 30 mg of soil per day.

^f Assumed to weigh 72.0 kg, to breathe 14.3 m³ of air per day, to drink 1.6 L of water per day and to ingest 30 mg of soil per day.

^g The ingestion of indoor dust is considered a significant source of indoor exposure to phthalates, including DIOP, and the amount of indoor dust ingested each day is based on Wilson et al. (2013). The median (6.6 µg/g) and 95th percentile (28.6 µg/g) of DIOP in indoor dust, was used for exposure characterization (personal communication from EHSRD, Health Canada, to ESRAB, Health Canada, August 2014).

Appendix E. Derivation of dietary intakes

Occurrence Data – DINP, DIDP, DMP, DIBP, DCHP, BBP, DBP, DEHP and DnHP

Phthalate occurrence data from the 2013 Canadian Total Diet Study (TDS) were prioritized for estimating dietary exposures. This dataset was determined to be the most comprehensive Canadian survey on the occurrence of phthalates in foods, and results were available for DiBP, BBP, DBP, and DEHP. For other phthalates, occurrence data in food were first taken from the 2013-2014 and 2014-2015 Food Safety Action Plan (FSAP) surveys conducted by the Canadian Food Inspection Agency (CFIA) and/or from a Total Diet Study conducted in the United States (US; Schecter et al. 2013), considering the similarity between samples analyzed in these studies and products available on the Canadian market. Occurrence data in foods that were not covered by the CFIA or the U.S. TDS datasets were supplemented by data from a British Total Diet Study (Bradley et al. 2013b). Note that these data were only used to fill data gaps and that duplicate occurrence data from the British TDS for a given food or phthalate were not included if such data were already available from the CFIA or the U.S. TDS datasets.

Results for phthalates in food that were reported as less than the analytical limit of detection (LOD) were assigned values of ½LOD. However, a value of 0 (zero) was assigned to all samples within a broad food category when no phthalates were detected above the LOD in any sample in that category.

The following table indicates the source(s) of occurrence data used to derive dietary exposure estimates for each phthalate.

Table E-1. Source of occurrence data

Phthalate	Canadian TDS (2013)	CFIA – FSAP (2013-2015)	Schecter et al. 2013 (U.S. TDS)	Bradley et al. 2013b (British TDS)
DiNP	-	X	-	X
DiDP	-	X	-	X
DMP	-	-	X	X
DiBP	X	-	-	-
DCHP	-	-	X	X
BBP	X	-	-	-
DBP	X	-	-	-
DEHP	X	-	-	-
DnHP	-	-	X	-

X = Source of occurrence data

- = No data

Note: DINP and DIDP intakes were unchanged from those presented in the SOS report. DIBP was monitored in Health Canada's 2013 TDS (Cao et al. 2015) however,

intakes using this new data showed no significant changes. For DCHP and DMP, the 2013 TDS data showed low detection frequencies; therefore, previous intake estimates are still presented in this draft screening assessment.

Food consumption data and matching to occurrence data

The phthalate concentrations in individual foods were matched to consumption figures for these foods from the 2004 Canadian Community Health Survey (CCHS) on nutrition (Statistics Canada 2004) to generate distributions of phthalate exposure for various age-sex groups. The CCHS included 24-hour dietary recall information for over 35,000 respondents of all ages across Canada.

Body weight information

For the purpose of determining per kilogram body weight exposure estimates, infant (0 to 1 year old) body weights were set to the mean body weights as derived from the body weight data from the United States Department of Agriculture Continuing Survey of Food Intakes by Individuals (1994-96 and 1998). For all other age groups, body weights reported in the CCHS, whether measured or self-reported, were used and where missing were imputed using the median for the corresponding age-sex group and quintile of energy intake.

Probabilistic exposure assessment

For each food consumed by a respondent in the CCHS, phthalate concentrations were randomly selected from the matching list of assayed values. For each individual respondent, exposure estimates from each food were summed, generating a distribution of exposure for all respondents. This was repeated 500 times (500 iterations) to model the variability of the distribution of exposures because of the variability of the phthalates levels. For each age-sex group, the median and 90th percentile exposures were derived from the empirical distribution generated by the 500 iterations.

Appendix F. Cumulative risk assessment total hazard index calculation

Table F-1. Summary of biomonitoring daily intakes for relevant subpopulations with highest exposure - phthalates in the Phthalate Substance Grouping

Phthalate	Age group (sex)	Intake (upper-bound; ug/kg bw/day)	Reference (i.e., CHMS, NHANES)
DIBP	3–5 years (M+F)	3.70	CHMS Cycle 2
DIBP	6–11 years (M+F)	5.30	CHMS Cycle 2
DIBP	19+ years (pregnant F)	1.20	P4
DCHP	3–5 years (M+F)	0	CHMS Cycle 2
DCHP	6–11 years (M+F)	0	CHMS Cycle 2
DCHP	12–19 years (F)	0	CHMS Cycle 2
DINP	2–3 years	5.2	MIREC-CD Plus
DINP	6–11 years (M)	25.00	NHANES (09-10)
DINP	12–19 years (F)	27.00	NHANES (09-10)

Table F-2. Summary of biomonitoring daily intakes for relevant subpopulations with highest exposure - additional phthalates

Phthalate	Age group (sex)	Intake (upper-bound; ug/kg bw/day)	Reference (i.e., CHMS, NHANES)
BBP	3–5 years (M+F)	4.50	CHMS Cycle 2
BBP	6–11 years (M)	3.4	CHMS Cycle 2
BBP	19+ years (pregnant F)	3.01	P4

DBP	3–5 years (M+F)	5.3	CHMS Cycle 2
DBP	6–11 years (F)	5.3	CHMS Cycle 2
DBP	19+ years (pregnant F)	4.11	P4
DEHP	3–5 years (M+F)	12.00	CHMS Cycle 2
DEHP	6–11 years (M)	12.00	CHMS Cycle 2
DEHP	18+ years (pregnant F)	8.42	MIREC

Table F-3. Summary of daily intakes for relevant subpopulations with highest exposure from environmental media and food - phthalates in the Phthalate Substance Grouping

Phthalate	Age group (sex)	Intake (upper- bound; ug/kg bw/day)	Type of exposure (i.e., food, dust, indoor air)
DIBP	0–6 months (M+F)	5.90	Food+dust+air+drinking water
DIBP	5–11 years (M+F)	0.78	Food+dust+air+drinking water
DIBP	12–19 years (M+F)	0.43	Food+dust+air+drinking water
DCHP	0.5–4 years (M+F)	0.15	Food+dust
DCHP	5–11 years (M+F)	0.12	Food+dust
DCHP	12–19 years (M+F)	0.07	Food+dust
DMCHP*	0–0.5 years (M+F)	0.05	Dust
DMCHP*	5–11 years (M+F)	0.02	Dust
DMCHP*	12–19 years (M+F)	0.00	Dust
DBzP*	0–0.5 years (M+F)	0.097	Dust

dSAR – Phthalate Substance Grouping

DBzP*	5–11 years (M+F)	0.032	Dust
DBzP*	12–19 years (M+F)	0.001	Dust
B84P	0–6 months (M+F)	0.05	Dust (B79P surrogate)
B84P	5–11 years (M+F)	0.02	Dust (B79P surrogate)
B84P	12–19 years (M+F)	0.00	Dust (B79P surrogate)
B79P	0–6 months (M+F)	0.05	Dust
B79P	5–11 years (M+F)	0.02	Dust
B79P	12–19 years (M+F)	0.00	Dust
DIHepP	0–6 months (M+F)	1.1	Dust
DIHepP	5–11 years (M+F)	0.37	Dust
DIHepP	12–19 years (M+F)	0.013	Dust
DINP	6 months– 4 years (M+F)	19.70	Food+dust
DINP	5–11 years (M+F)	14.90	Food+dust
DINP	12–19 years (M+F)	11.43	Food+dust
CHIBP	NIC	NIC	NIC
BCHP	NIC	NIC	NIC
BIOP	NIC	NIC	NIC

NIC = Not in commerce

*NIC but detected in Canadian house dust

Table F-4. Summary of daily intakes for relevant subpopulations with highest exposure from environmental media and food - additional phthalates

Phthalate	Age group (sex)	Intake (upper-bound; ug/kg bw/day)	Type of exposure (i.e., food, dust, indoor air)
BBP	6 months–4 years (M+F)	2.99	Food+dust+air+drinking water+soil
BBP	5–11 years (M+F)	1.48	Food+dust+air+drinking water+soil
BBP	12–19 years (M+F)	0.49	Food+dust+air+drinking water+soil
DBP	6 months–4 years (M+F)	2.96	Food+dust+air+drinking water+soil
DBP	5–11 years (M+F)	1.83	Food+dust+air+drinking water+soil
DBP	12–19 years (M+F)	1.23	Food+dust+air+drinking water+soil
DEHP	0.5–4 years (M+F)	27.57	Food+dust+air+drinking water+soil
DEHP	5–11 years (M+F)	17.60	Food+dust+air+drinking water+soil
DEHP	12–19 years (M+F)	10.10	Food+dust+air+drinking water+soil
DnHP*	0–6 months (M+F)	0.31	Food+dust
DnHP	5–11 years (M+F)	0.136	Food+dust
DnHP	12–19 years (M+F)	0.031	Food+dust
DIOP	0–6 months (M+F)	0.14	Dust
DIOP	5–11 years (M+F)	0.05	Dust
DIOP	12–19 years (M+F)	0.002	Dust

*NIC but detected in Canadian house dust

Table F-5. Critical effect levels for medium-chain phthalates in the Phthalate Substance Grouping

Phthalate	Life stage	NOAEL (mg/kg bw/day)	Effects (duration); (reference)	Default uncertainty factor	Calculated reference value
DIBP	In utero	125	Reduced AGD, NR, effects on fertility (GD12-21), ↓ testicular testosterone; (Saillenfait et al. 2008; Furr et al. 2014)	100	1.25
DIBP	(Pre)pubertal	300	Testicular pathology (PND21-28, 7 days); (Zhu et al. 2010)	300	1
DCHP/ DMCHP	In utero	10–20 (LOAEL)	↓ AGD, TP, increase resorption (GD6-19); (Ahabab and Barlas 2015; Li et al. 2016; Hoshino et al. 2005)	100	0.1
DCHP/ DMCHP	(Pre)pubertal	18	↓ spermatid head counts, testicular atrophy, ↓ body weight gain, ↓ food consumption in F1 males; (Hoshino et al. 2005)	300	0.06
DBzP (MBzP)	In utero	167	Read across from MBzP ↓ AGD (~10%) and ↑ cryptorchidism (GD15-17); (Ema et al. 2003)	100	1.67
DBzP (MBzP)	(Pre)pubertal	250 (LOEL)	Read across from MBzP ↓ sperm count (20%) (4 weeks); (Kwack et al. 2009)	300	0.833
B84P (BBP)	In utero	50	Read across from BBP Decreased pup body weight, decreased ↓AGD at birth in F2 (based on two-generation studies) ↓ testicular testosterone levels (GD14-18);	100	0.5

			(Aso et al. 2005; Nagao et al. 2000; Tyl et al. 2004; Furr et al. 2014)		
B84P (BBP)	(pre)pubertal	250– 500 (LOEL)	Read across from MBzP and BBP ↓ sperm count (20%) (4 weeks); (Kwack et al. 2009)	300	0.833
B79P	In utero	50	↓ AGD and ↑ epispadias (GD6-PND21) (REACH dossier; (ECHA 2013b); ECHA 2013b)	100	0.5
B79P	(Pre)pubertal	375	No adverse effects at the highest dose tested; Tyl et al. 2013	300	1.25
DIHepP	In utero	64–168	significant reduction in AGD (13%) in male F ₂ pups (2 gen); (McKee et al. 2006)	100	0.64
DIHepP	(Pre)pubertal	227– 416	Significant reduction in AGD. Delayed PPS, ↑ nipple retention, hypospadias and cryptorchidism in F1 pups (2 gen); (McKee et al. 2006)	300	0.757
DINP	In utero	10 (LOEL)	MNGs, Leydig cell clusters/aggregation (GD12-21); (Li et al. 2015)	100	0.1
DINP	(Pre)pubertal	500 (LOEL)	Decreased absolute seminal vesicle and LABC weights (10 days), castrated animals; (Lee and Koo 2007)	300	0.333

Table F-6. Critical effect levels for additional phthalates

Additional phthalate	Life stage	NOAEL (mg/kg bw/d)	Effects (duration); (reference)	Reference	Default uncertainty factor	Calculated reference value
BBP	In utero	50	↓AGD at birth in F2 (based on two two-generation studies); Aso et al. 2005; (Tyl et al. 2004; Nagao et al. 2000)	Aso et al. 2005; Tyl et al. 2004; Nagao et al. 2000	100	0.5
BBP	(Pre)pubertal	500 (LOEL)	↓ sperm count (30%), ↓ sperm motility, ↓ body weight gain, ↑ rel. liver weight (4 weeks); (Kwack et al. 2009)	Kwack et al. 2009	300	1.667
DBP	In utero	10	↓ testicular testosterone (GD12-19), fertility effects (GD14-23.5), ↓ in tubular and interstitial cell populations, altered seminiferous tubule morphometry, other mild effects on spermatocyte development (GD12-21); (Lehmann et al. 2004; Ahmad et al. 2014; Boekelheide et al. 2009)	Lehmann et al. 2004; Ahmad et al. 2014; Boekelheide et al. 2009	100	0.1
DBP	(Pre)pubertal	10–50 (LOEL)	LOEL: delayed spermatogenesis, reduced absolute AGD (relative to BW at higher dose) in mice (PND 4-14); (Moody et al. 2013; Srivastava et al. 1990; Xioa-feng et al. 2009)	Moody et al. 2013; Srivastava et al. 1990; Xioa-feng et al. 2009	300	0.033
DEHP	In utero	4.8	Small and/or aplastic epididymis, testicular pathology other RPS effects in F1 and F2 (2-gen study); (Blystone et	Blystone et al. 2010; Wolfe and Layton 2003; Andrade et	100	0.048

			al. 2010; Wolfe and Layton 2003; Andrade et al. 2006a,b; Christiansen et al. 2010)	al. 2006a,b; Christiansen et al. 2010		
DEHP	(Pre)pubertal	10	↓ absolute and relative testis weight (>10%) (PND 6-10, 5 days exposure); (Dostal et al. 1988)	Dostal et al. 1988	300	0.033
DnHP	In utero	5	↓ serum/ testicular testosterone levels, ↓ AGD, testicular pathological changes (GD12-19, GD 6-19); (Ahabab and Barlas 2015; Saillenfait et al. 2013)	Ahabab and Barlas 2015; Saillenfait et al. 2013	100	0.05
DnHP	(Pre)pubertal	10	Read across from DEHP ↓ absolute and relative testis weight (>10%) (PND6-10, 5 days exposure); (Dostal et al. 1988)	Dostal et al. 1988	300	0.033
DIOP	In utero	100	testicular pathological changes, fertility effects and ↓ testis weight (GD12-19, GD12-21, GD6-19); (Saillenfait et al. 2013)	Saillenfait et al. 2013	100	1
DIOP	(Pre)pubertal	227–416	Read across from DIHepP Significant reduction in AGD. Delayed PPS, ↑ nipple retention, hypospadias and cryptorchidism in F1 pups (2 gen study); (McKee et al. 2006)	McKee et al. 2006	300	0.757

Table F-7. Individual HQs and total HI for pregnant women and women of childbearing age

Phthalate	Environmental media and food; hazard quotient (% of HI)	Biomonitoring; hazard quotient (% of HI)
DIBP	0.0003 (0.1%)	0.0010 (0.4%)
DCHP	0.0007 (0.3%)	0.0000 (0.0%)
DMCHP	0.0000 (0.0%)	N/A
DBzP	0.0000 (0.0%)	N/A
B84P	0.0000 (0.0%)	N/A
B79P	0.0000 (0.0%)	N/A
DIHepP	0.0000 (0.0%)	N/A
DINP	0.0072 (3.1%)	0.0170 (7.1%)
CHIBP	0.0000 (0.0%)	N/A
BCHP	0.0000 (0.0%)	N/A
BIOP	0.0000 (0.0%)	N/A
BBP	0.0010 (0.4%)	0.0060 (2.5%)
DBP	0.0123 (5.3%)	0.0411 (17.1%)
DEHP	0.2104 (90.5%)	0.1754 (72.9%)
DnHP	0.0006 (0.3%)	N/A
DIOP	0.0000 (0.0%)	N/A
HI for pregnant women	0.23	0.24

N/A = Not applicable

Table F-8. Individual HQs and total HI for infants

Phthalate	Environmental media and food; hazard quotient (% of HI)	Biomonitoring; hazard quotient (% of HI)
DIBP	0.0047 (0.6%)	0.0030 (0.8%)
DCHP	0.0015 (0.2%)	0.0000 (0.0%)
DMCHP	0.0002 (0.0%)	N/A
DBzP	0.0001 (0.0%)	N/A
B84P	0.0001 (0.0%)	N/A
B79P	0.0001 (0.0%)	N/A
DIHepP	0.0017 (0.2%)	N/A
DINP	0.1970 (24.0%)	0.0520 (14.2%)
CHIBP	0.0000 (0.0%)	N/A
BCHP	0.0000 (0.0%)	N/A
BIOP	0.0000 (0.0%)	N/A
BBP	0.0060 (0.7%)	0.0090 (2.5%)
DBP	0.0296 (3.6%)	0.0530 (14.4%)
DEHP	0.5743 (70.0%)	0.2500 (68.1%)
DnHP	0.0062 (0.8%)	N/A
DIOP	0.0001 (0.0%)	N/A
HI for infants	0.82	0.37

N/A = Not applicable

Table F-9. Individual HQs and total HI for children

Phthalate	Environmental media and food; hazard quotient (% of HI)	Biomonitoring; hazard quotient (% of HI)
DIBP	0.0008 (0.1%)	0.0053 (1.0%)
DCHP	0.0020 (0.3%)	0.0000 (0.0%)
DMCHP	0.0003 (0.0%)	N/A
DBzP	0.0000 (0.0%)	N/A
B84P	0.0000 (0.0%)	N/A
B79P	0.0000 (0.0%)	N/A
DIHepP	0.0015 (0.3%)	N/A
DINP	0.0089 (1.5%)	0.0150 (2.8%)
CHIBP	0.0000 (0.0%)	N/A
BCHP	0.0000 (0.0%)	N/A
BIOP	0.0000 (0.0%)	N/A
BBP	0.0009 (0.1%)	0.0020 (0.4%)
DBP	0.0555 (9.1%)	0.1590 (29.4%)
DEHP	0.5333 (87.4%)	0.3600 (66.5%)
DnHP	0.0041 (0.7%)	N/A
DIOP	0.0001 (0.0%)	N/A
HI for children	0.61	0.54

N/A = Not applicable